



Brain-heart interactions are modulated across the respiratory cycle via interoceptive attention

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ABSTRACT

Respiration and heartbeat continuously interact within the living organism at many different levels, representing two of the main oscillatory rhythms of the body and providing major sources of interoceptive information to the brain. Despite the modulatory effect of respiration on exteroception and cognition has been recently established in humans, its role in shaping interoceptive perception has been scarcely investigated so far.

In two independent studies, we investigated the effect of spontaneous breathing on cardiac interoception by assessing the Heartbeat Evoked Potential (HEP) in healthy humans. In Study 1, we compared HEP activity for heartbeats occurred during inhalation and exhalation in 40 volunteers at rest. We found higher HEP amplitude during exhalation, compared to inhalation, over fronto-centro-parietal areas. This suggests increased brain-heart interactions and improved cortical processing of the heartbeats during exhalation. Further analyses revealed that this effect was moderated by heart rate changes. In Study 2, we tested the respiratory phase-dependent modulation of HEP activity in 20 volunteers during Exteroceptive and Interoceptive conditions of the Heartbeat Detection (HBD) task. In these conditions, participants were requested to tap at each heartbeat, either listened to or felt, respectively. Results showed higher HEP activity and higher detection accuracy at exhalation than inhalation in the Interoceptive condition only. Direct comparisons of Interoceptive and Exteroceptive conditions confirmed stronger respiratory phase-dependent modulation of HEP and accuracy when attention was directed towards the interoceptive stimuli. Moreover, HEP changes during the Interoceptive condition were independent of heart physiology, but were positively correlated with higher detection accuracy at exhalation than inhalation. This suggests a link between optimization of cortical processing of cardiac signals and detection of heartbeats across the respiratory cycle.

Overall, we provide data showing that respiration shapes cardiac interoception at the neurophysiological and behavioural levels. Specifically, exhalation may allow attentional shift towards the internal bodily states.

1. Introduction

Respiration and heartbeat are inextricably interconnected. Together, they produce two of the dominant oscillatory rhythms of the organism and represent major sources of interoceptive information (Chen et al., 2021; Khalsa et al., 2009; Weng et al., 2021). Interoception has been commonly defined as the process by which the brain receives, elaborates and interprets signals originating from the peripheral organs, continuously updating the conscious and (mostly) unconscious representations of the physiological condition of the body (Berntson and Khalsa, 2021; Craig, 2003; Critchley et al., 2004). However, within the field of intero-

ception research, respiratory and cardiac signals processing have been studied mainly separately so far. In addition, there is no question that cardiac interoception has attracted most of the attention in the field.

Cardiac interoceptive signal processing is known to modulate higher-order cognition (Azzalini et al., 2019), as well as the processing of external sensory information (Skora et al., 2022), and is also related to the state of consciousness (Candia-Rivera et al., 2021). Since Schandry's first proposal (Schandry, 1981), various behavioural tasks have been proposed to assess the individual interoceptive accuracy, as the ability to voluntarily focus on one's own heart and correctly report its beating. Importantly, research has shown that higher sensitivity to car-

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diac signals supports the capacity to regulate emotions and behaviour (Dunn et al., 2007; Herbert et al., 2011; Herbert et al., 2012; Herbert and Pollatos, 2014; Wiens, 2005), while it is negatively associated to the susceptibility to mental health problems (de la Fuente et al., 2019; Lutz et al., 2019; Schulz et al., 2015; Yoris et al., 2017).

However, heartbeat sensations remain for the most part outside of the field of awareness, and theoretical and methodological limitations of cardiac interoception have emerged (Brener and Ring, 2016; Garfinkel et al., 2022). For instance, a recent meta-analysis on 133 independent studies on heartbeat detection questioned the link between cardiac interoceptive accuracy and mental health outcomes (Desmedt et al., 2022). Additionally, heartbeat counting task accuracy scores have been found to be confounded by heart frequency, both real (Ring et al., 1994; Zamariola et al., 2018) and estimated by participants (Desmedt et al., 2018), as well as by prior beliefs on one's own heartbeat frequency (Brener and Ring, 2016; Murphy et al., 2018; Windmann et al., 1999).

More recently, researchers have increasingly focused on a more objective, electrophysiological index of the cortical processing of single heartbeats, the so-called Heartbeat Evoked Potential (HEP). The HEP is an Electroencephalographic (EEG) event-related potential, time-locked to participants' Electrocardiogram (ECG) R-peak or T-peak (Pollatos and Schandry, 2004). Physiological pathways underlying the HEP are mostly unknown, but they likely involve signals originating from baroreceptor activity (Gray et al., 2007; Garfinkel and Critchley, 2016). Baroreceptors are stretch receptors located near the aortic arch and the carotid arteries, whose discharge activity is time-locked to cardiac systole and is driven by rhythmic changes in arterial blood pressure (Park and Blanke, 2019a). Baroreceptor-mediated information is sent upstream via the vagus nerve to the nucleus of the solitary tract in the brainstem and to the ventromedial posterior nucleus of the thalamus. Cardiac interoceptive information is finally elaborated in the brain at the level of the insula, amygdala, anterior cingulate, and somatosensory cortices, which represent the main cerebral sources of HEP activity (Canales-Johnson et al., 2015; Kern et al., 2013; Park and Tallon-Baudry, 2014). Importantly, HEP activity increases when individuals voluntarily orient their attention to the heartbeat (García-Cordero et al., 2017; Mai et al., 2018; Petzschner et al., 2019; Salamone et al., 2018; Villena-González et al., 2017), and is also positively associated to their accuracy in detecting heartbeats during cardiac interoceptive tasks (Canales-Johnson et al., 2015; Marshall et al., 2017; Pollatos et al., 2005). However, there are several other mechanisms underlying the HEP that are currently understudied, such as somatosensory receptors activity related to subtle skin movements, afferent cardiac neurons activation, and neuro-vascular coupling at the cortical level (Tallon-Baudry et al., 2018; Park and Blanke, 2019a). Therefore, physiological pathways underlying heartbeat processing and perception likely involve both interoceptive and exteroceptive (e.g., somatosensory) signals (Khalsa et al., 2009; Galvez-Pol et al., 2022).

In line with the inextricable interconnection between heartbeat and respiration, separate studies have independently shown that both HEP and cardiac interoceptive accuracy are modulated by respiration. For instance, one study from Baumert et al. (2015) assessed respiratory phase-dependent (inhale vs. exhale) HEP peak amplitude in children with sleep disordered breathing during REM sleep. The authors found decreased peak HEP amplitude during exhalation in the sleep disordered breathing group. Moreover, MacKinnon and colleagues (2013) observed increased peak HEP amplitude over central EEG electrodes during "resonant breathing" (i.e., breathing at a rate of 6 breaths per minute), compared to spontaneous breathing. Finally, two recent studies (Smith et al., 2020, 2021) consistently showed that breath-holding can improve participants' cardiac interoceptive accuracy, as assessed with a modified version of the Heartbeat Detection (HBD) task. However, all these studies investigated the effect of respiration on HEP changes and interoceptive accuracy separately and in a "perturbed" physiological setting, that is during systemic alteration of respiratory activity (REM sleep, slow breathing, and breath-hold). A systematic and multilevel investigation

of the complex neuro-cardio-respiratory interactions (Corcoran et al., 2018) in an "ecological" setting is still lacking. This would allow the simultaneous characterization of the effects of spontaneous breathing on both HEP and interoceptive accuracy, as well as their possible relationship.

Spontaneous breathing occurs mostly outside of the field of awareness and comprises a phase of active inspiration, that involves the contraction of the diaphragm and the external intercostals muscles, and a phase of passive expiration due to their subsequent relaxation. However, unlike the heartbeat, breathing can be easily accessed consciously and voluntarily controlled in its depth and frequency (Del Negro et al., 2018; Feldman et al., 2013). Respiration represents one of the most salient conscious forms of interoception. Despite this, it has received relatively low scientific interest until very recently, when increasing evidence has been accumulating about respiratory phase-dependent changes of brain activity, perception, and cognitive-emotional functions in both animals and humans (see Tort et al., 2018 for an extensive review). In humans, spontaneous respiration seems to drive the oscillatory activity of a wide range of neural network at rest (Kluger and Gross, 2021). In turn, respiratory-driven brain activity can modulate sensorimotor, cognitive, and emotional processes (Folschweiller and Sauer, 2021). For example, Zelano et al. (2016) found increased emotional recognition and episodic memory encoding and retrieval during inhalation, compared to exhalation. Furthermore, phase-locking of stimulus onset to inhalation increased participant's near-threshold somatosensory perception (Grund et al., 2022) visuospatial recognition abilities (Kluger et al., 2021; Perl et al., 2019), and memory performance (Huijbers et al., 2014). Differently, self-initiated motor actions (Park et al., 2020), and trace eyeblink conditioning learning (Waselius et al., 2019) were more frequent during exhalation, while the exhalation-to-inhalation phase transition improved recognition memory performance (Nakamura et al., 2018). Based on this and other evidence, within the framework of predictive coding theories of brain functioning (Clark, 2013; Friston, 2010), respiration has been recently interpreted as a form of "active sensing" (Allen et al., 2021; Boyadzhieva and Kayhan, 2021; Corcoran et al., 2018). Active sensing conceptualises individuals as active seekers of exteroceptive information from the environment. Recent studies on the cardiac system have shown that active visual and somatosensory perception is improved during the cardiac diastolic phase (i.e., the quiescent periods of the cardiac cycle, Galvez-Pol et al., 2020, 2022), suggesting that exteroceptive information sampling is regulated by interoception. Similarly, for what concerns respiration, there is evidence showing that neuronal excitability is rhythmically increased during inhalation (compared to exhalation) to adaptively align bottom-up sensory information with top-down predictive streams (Corcoran et al., 2018). This process ends in the amplification of exteroceptive sensory information from the environment during the most active phase of respiration, namely, inhalation (Tort et al., 2018).

Thus, the question arises as to whether spontaneous respiration plays a role in shaping the processing of interoceptive information generated from inside the body as well. In particular, the role of the respiratory phases assumes a special psychophysiological interest in the context of cardiac interoception for the following reasons: first, heartbeat and respiration are deeply linked at the body level, given the coupling between respiratory cycle and baroreceptor activity. This interaction is commonly observed during respiratory phase-dependent heart rate changes known as Respiratory Sinus Arrhythmia (RSA, Brecher and Hubay, 1955). Second, heartbeat and respiration share similar interoceptive pathways, both reaching the central nervous system through the vagus nerve at the level of the anterior and posterior insula, hippocampus, precuneus, somatosensory, and cingulate cortices (Farb et al., 2013; Wang et al., 2019), suggesting the possibility that respiratory and cardiac interoceptive signals interact also at the brain level, with possible effects on the individual interoceptive accuracy.

Therefore, the aim of the present work is twofold: i) to investigate and characterize respiratory phase-dependent modulations of neural re-

sponses to single heartbeats, as measured by HEP activity at rest; and ii) to relate respiratory phase-dependent HEP modulations to cardiac interoceptive attention. To fulfil these objectives, we performed two independent studies, simultaneously recording participant's EEG, ECG, and respiratory activity. In Study 1, we tested 40 healthy volunteers during a resting-state condition, while in Study 2 we tested 20 healthy volunteers during the performance of the HBD task, which requires to focus attention on the heart and tap a button in synchrony with each heartbeat.

2. Materials and methods

2.1. Ethics statement

The studies were approved by the Institutional Review Board of Psychology, Department of Psychological, Health and Territorial Sciences, "G. d'Annunzio" University of Chieti-Pescara (Protocol Number 44_26_07_2021_21016), in compliance with the Italian Association of Psychology and the Declaration of Helsinki guidelines and its later amendments. All subjects signed a written informed consent.

2.2. Data and code availability

The code used to analyze the experiment is available in an open repository at the following link: https://github.com/azaccaro90/HEP_respiration.git. The behavioral and physiological raw data can be shared by the corresponding author upon request if data privacy can be guaranteed according to the rules of the European General Data Protection Regulation (EU GDPR). The repository also contains anonymized data from a participant that took part in Study 1 and Study 2.

2.3. Study 1 – resting-state condition

2.3.1. Participants

Forty healthy volunteers with normal or corrected-to-normal vision (29 females; two left-handed; age: 26.67 ± 4.56 years [mean \pm SD]) took part in the study. We estimated the sample size through the G*Power 3 software (v3.1.9.7; Faul et al., 2007) based on the results of a recent meta-analysis on HEP activity (Coll et al., 2020). We estimated a medium effect size of Cohen's $d = 0.5$, set the significance level to $\alpha = 0.05$, and the desired power at 0.80 (estimated sample size = 34). The inclusion of each volunteer was based on the following criteria as self-reported: i) no personal or family history of neurological, psychiatric, or somatic disorders; and ii) not having taken any drug acting on the central nervous system in the previous week. One participant was excluded from EEG analysis because of excessive movement-related artifacts.

2.3.2. Experimental procedure

Participants were asked to rest for 10 minutes with eyes open while watching at a fixation cross at the centre of a computer screen and letting their mind wander (Raichle et al., 2001). No specific instruction on breathing was given, and participants were blind to the experimental goals. EEG, ECG, and respiratory signals were simultaneously recorded throughout the session. Before starting the session, participants had to verbally confirm that they could not feel their heartbeat through the respiratory belt, in case the belt was wrongly mounted too tight.

2.3.3. Electrophysiological recordings

EEG signal was recorded from 64 scalp electrodes using a BrainAmp EEG acquisition system (BrainCap MR, BrainVision, LLC), according to the international 10-20 system. The midfrontal electrode (FCz) was used as the reference and the inion electrode (Iz) as the ground. Electrode impedance was kept below 10 k Ω for all channels. ECG data were obtained from three ECG electrodes, two placed over the left and right clavicles, and the ground located on the right costal margin (MP160

BIOPAC Systems, Inc). Another ECG electrode, that was integrated in the EEG net, was placed on the left breast, serving as a backup. Respiratory activity was recorded via a respiratory belt positioned around the chest (respiratory transducer TSD201, BIOPAC Systems, Inc). All signals were recorded with a sampling rate of 2 kHz; band-pass filtering from 0.016 to 250 Hz was applied, along with 50 Hz notch filtering.

2.3.4. Electrophysiological data pre-processing

ECG and respiratory signals were high-pass filtered (0.1 Hz) to remove baseline fluctuations. A low-pass filter at half the resampling frequency (i.e., 128 Hz) was applied to the data to avoid aliasing effects, then signals were down-sampled to 256 Hz. To perform HRV measurements, R-peaks were extracted from the ECG and analyzed using the Pan-Tompkins algorithm (Pan and Tompkins, 1985; Sedghamiz, 2014), separately from the EEG data. Mis-detected peaks (less than 1%) were corrected using a point process model (Citi et al., 2012). The obtained RR-interval data set (tachogram) was processed using Kubios free software (v3.4.3, Tarvainen et al., 2014) and a set of Heart Rate Variability (HRV) features of interest were extracted. Time-domain parameters, such as Heart Rate (HR), and frequency-domain parameters, such as power in High-Frequency band (HF - 0.15-0.4 Hz) log value (Malik et al., 1996), Heart Rate Variability (HRV) total power, and Low-Frequency/High-Frequency ratio (LF/HF) (Supplementary Material 1) were computed. Respiratory signals were processed using BreathMetrics (Noto et al., 2018) toolbox algorithms, to extract inhale and exhale onsets and offsets, as well as the set of respiratory features of interest, such as breathing rate, average inhale duration, average exhale duration, Inhalation/Exhalation (I/E) ratio (Supplementary Material 1). Inhale and exhale onsets and offsets were then visually inspected, and noisy breathing cycles were manually rejected. A respiratory cycle was defined as starting from the beginning of an inhalation and ending at the beginning of the next inhalation.

EEG data were pre-processed offline using EEGLAB (v2021.1; Delorme and Makeig, 2004) toolbox algorithms running on a MATLAB environment (R2021a, MathWorks Inc.). After all individual blocks were concatenated, signals were down-sampled to 256 Hz. Before resampling, a low-pass filter at half the resampling frequency (i.e., 128 Hz) was applied to the data to avoid aliasing effects. Datasets were then filtered using a Hamming windowed FIR filter (0.5-40 Hz). Signals were visually inspected for the removal of artefacts and the detection of noisy channels. Bad segments were manually rejected. Noisy EEG channels were then removed and interpolated using their neighbouring channels (Al et al., 2021; Junghöfer et al., 2000). Rejected channels were generally few (~5%, depending on the EEG recording). Retained signal was submitted to Independent Component Analysis to visualize and manually remove sources of heartbeat, ocular, and muscle artifacts (FastICA algorithm; Hyvärinen, 1999). Particular attention was given to cardiac field artifact (CFA), by visually selecting the components whose activities followed the time course of R-peak of the ECG (Al et al., 2020, 2021) (Supplementary Material 2, Supplementary Fig. 1). EEG signals were finally re-referenced to the average of all channels (Candia-Rivera et al., 2021).

2.3.5. HEP analysis

HEPs were analysed using ERPLAB toolbox algorithms (v8.30; Lopez-Calderon and Luck, 2014). HEP was computed on EEG signals time-locked to the T-peak of the ECG (Babo-Rebelo et al., 2019; Babo-Rebelo et al., 2016; Park et al., 2014). ECG T-peak positions were identified using the HEPLAB toolbox (Perakakis, 2019). Automatic detection of T-peaks was performed on the filtered ECG signal (not previously corrected with the ectopic heartbeat correction algorithm), to avoid heartbeat timing displacements. Detection of T-peaks was followed by visual inspection and manual correction of misdetected peaks (Al et al., 2021). EEG data were epoched and baseline-corrected between -100 and 0 ms, using the T-peak event as temporal reference (epoch length: -100 to 350 ms after T-peak) (Park et al., 2014). The time window of interest

for the statistical analysis was set to 80-350 ms, coincident with cardiac relaxation, when the CFA is minimum (Babo-Rebello et al., 2019; Babo-Rebello et al., 2016; Dirlich et al., 1997). Additionally, we rejected all epochs in which the signal recorded at any channel exceeded a threshold of 100 μV (Blankenship et al., 2018; Villena-González et al., 2016), using a moving window peak-to-peak threshold function implemented in ERPLAB (moving window size: 200 ms; step size: 100 ms) (Lopez-Calderon and Luck, 2014). The number of rejected epochs was less than 1%. Artifact-free epochs were assigned to “inhale” if the respective T-peak fell within the inhale onset/inhale offset time range, and to “exhale” if the T-peak fell within the exhale onset/exhale offset time range. HEP corresponding to inhale and exhale were computed for each participant by averaging EEG epochs assigned to the respective respiratory phase. We analysed HEP epochs (-100 to 350 ms around T-peak) occurring exclusively during inhalation or exhalation, that is, excluding those occurring across both respiratory phases, to avoid uncontrolled effects due to inhalation or exhalation onset (e.g., respiratory-related evoked potentials; Davenport et al., 2007; Webster and Colrain, 2000). Finally, we excluded epochs including T-peaks followed by an R-peak by less than 350 ms, to avoid overlap between the HEP activity and the following R-peak residual CFA (Babo-Rebello et al., 2019).

HEP differences between respiratory phases were statistically assessed in the EEG artifact-free time window 80–350 ms after the T-peak, using a cluster-based permutation t-test implemented in the Field-Trip toolbox (Oostenveld et al., 2011). First, paired t-values were calculated by comparing the “inhale” and “exhale” phases in the 80-350 ms time window. Clusters were then formed by pooling together all data points adjacent in both time (i.e., contiguous time-points) and space (i.e., neighbouring channels) with a p-value below 0.05 within the time window of interest. The t-statistic of each cluster was obtained by summing all t-values within the cluster. Then, a randomized null distribution of cluster-level t-statistics was obtained with a Monte Carlo permutation procedure that randomly shuffled the “inhale” and “exhale” phase labels 10000 times, and entered into the null distribution the largest obtained cluster-level statistic for each randomization. Finally, statistical significance was calculated by comparing the experimentally observed cluster-level statistics with the randomly-generated null distribution. This procedure inherently corrects for multiple comparisons in time and space, and clusters with a corrected p-value below 0.05 were considered significant (two-tails). On average, there were 5.4 neighbours per channel, with minimum number of neighbouring channels for forming a cluster (i.e., `cfg.minnbchan`) set at 2. We did not use any a priori spatial or temporal region of interest for the comparison between inhale and exhale HEP, hence including the entire EEG sensor space and epoch time window (80-350 ms) (Petzschner et al., 2019).

In addition, since traditionally the HEP is computed by epoching EEG data around the R-peaks, we re-analysed our data using the R-peak as a time reference (See Supplementary Material 3).

2.3.6. Source analysis

A standard structural T1-weighted MRI template (ICBM152) (Fonov et al., 2009) was used to estimate the neural sources of the EEG signals within the BrainStorm toolbox (v3.210416; Tadel et al., 2011). Lead field matrix were computed with a 3-shell Boundary Element Model using the OpenMEEG (Gramfort et al., 2010; Kybic et al., 2005) toolbox. Then, neural sources were estimated following the Minimum Norm Estimation method using sLORETA normalization (Pascual-Marqui, 2002), by keeping constrained current dipole orientations (i.e., normally oriented) with respect to the cortical surface. The cortex surface was downsampled to 15000 vertices (one for each dipole). For the statistical test of the neural sources of differential HEP amplitudes among respiratory phases (inhale vs. exhale), we used cluster-based statistics in the source space (1000 randomizations) from the FieldTrip toolbox (Oostenveld et al., 2011).

2.3.7. Additional cardiorespiratory analyses during resting-state

To investigate the possible explanatory role of cardiac and respiratory physiology on HEP modulation among respiratory phases, we performed a series of additional analyses at the trial level, when possible (i.e., instantaneous HR, ECG signal, and HEP activity), otherwise at the subject level.

At the subject level, we first calculated HR for each participant in each respiratory phase, and compared HR during inhalation with HR during exhalation with a paired t-test, looking for the well-known RSA effect. Regarding the ECG, we compared the averaged ECG signal time-locked to the T-peak of inhale phases with that of exhale phases with a repeated-measures, two-tailed t-test within the time window of observed significant HEP differences (Groppe et al., 2011), corrected with the False Discovery Rate (FDR, Benjamini and Yekutieli, 2001) procedure. Finally, we calculated a ΔHEP index for each participant (by subtracting the mean HEP value during inhale from the mean HEP value during exhale in the significant time window, averaged within the cluster of significant electrodes), and then we correlated the ΔHEP index with the set of cardiac and respiratory features of interest (Supplementary Material 1).

At the single-trial level, we assessed the effects of our experimental manipulations with a linear mixed-effect model analysis implemented in jamovi (v2.2.2; The jamovi project, 2021) in the General Analyses for the Linear Model (GAMLj) module (Gallucci, 2019). This mixed-effect modelling allowed us to test for the effects of the respiratory phase on HEP activity by controlling for instantaneous HR and trial-based ECG activity, with a significant gain in statistical power (Kliegl et al., 2010; Ambrosini et al., 2019) (See Supplementary Material 4).

2.4. Study 2 - heartbeat detection task

2.4.1. Participants

Twenty healthy volunteers that participated in Study 1 were recruited for the study (14 females; two left-handed; mean age: 25.21 ± 2.64 years [mean \pm SD]). Sample size was estimated through G*Power 3 (v3.1.9.7; Faul et al., 2007) based on the results of a previous study investigating HBD task accuracy (Fittipaldi et al., 2020). We estimated a medium/high effect size of Cohen's $d = 0.8$, set the significance level to 0.05, and the power at 0.80 (estimated sample size = 15). Inclusion criteria were the same as in Study 1. One participant was excluded from EEG analysis because of excessive movement-related artifact.

2.4.2. Experimental procedure

Following a brief training, participants were asked to perform the two conditions of a validated HBD task (Fittipaldi et al., 2020; García-Cordero et al., 2017; Yoris et al., 2017). In the first condition, named Exteroceptive Condition (EC), participants were presented with digitally constructed heartbeat sounds and instructed to press a button in synchrony with it using their dominant hand. They were given the following instructions: “You will hear the beating of a heart. Tap the button with your dominant hand as soon as you hear each heartbeat. Please avoid anticipated responses by guessing the recorded heart rhythm”. The EC consisted of 4 blocks, each lasting 2.5 minutes, for a total of 10 minutes. In two blocks the heartbeats were presented at a regular frequency (60 bpm), while in the rest of the blocks the heartbeats were presented with irregular heartbeat intervals (60 bpm, on average). In the second condition, named Interoceptive Condition (IC), participants were asked to focus their attention on their heart and tap a button in synchrony with their own heartbeats, in the absence of any external cues. Instructions were as follows: “Now, you must follow the beating of your own heart by tapping a button with your dominant hand for every beat you feel. You should not guide your responses by checking your arterial pulse in your wrists or neck. If you are unable to feel these sensations, you should appeal to your intuition trying to respond whenever you think your heart is beating” (Fittipaldi et al., 2020). The IC consisted of 4 blocks lasting

2.5 min each, for a total of 10 minutes. As in Study 1, during both conditions, participants kept their eyes open and watched a fixation cross at the centre of the monitor. No specific instructions on breathing were given. EEG, ECG, and respiratory signals were simultaneously recorded throughout IC and EC.

2.4.3. Electrophysiological recordings, signals pre-processing, and HEP analysis

We applied the same analysis pipeline of Study 1 for recording EEG and cardiorespiratory signals, as well as for EEG data pre-processing and analysis of the HEP time-locked to the T-peaks. HEP analysis on the R-peak was not performed during Study 2. In fact, participants' tapped responses fell within the same time window of significant respiratory phase-related HEP effects observed when time-locking the epochs on the R-peak (on average, around 335 ms after the R-peak, see Supplementary Material 8). In order to avoid confounding effects due to motor tapped responses during the HBD task, we focused exclusively on T-peak time-locked HEP epochs.

2.4.4. Task accuracy assessment and comparison

Participants' interoceptive accuracy was assessed by calculating the interoceptive accuracy index, based on previously reported standard procedures (Fittipaldi et al., 2020; García-Cordero et al., 2017; Yoris et al., 2017). Correct answers were estimated by time-locking participant's tapped responses with a corresponding time window around each R-peaks registered by the ECG. In line with canonical procedures, we first time-locked every tapped response to the participants' ECG. Next, we calculated a "window of accurate response" after each R-peak. These time windows varied in length depending on the participant's HR. That is, they were longer for slower HR, and shorter for higher HR (Melloni et al., 2013). Unlike canonical procedure, which calculates the time windows of accurate response depending on mean HR, to control for HR differences between participants in the IC, we relied on the participants' instantaneous HR. Instantaneous HR (bpm) was calculated for

each R-peak based on the time from the current R-peak of the heart wave to the R-peak point of the next wave. This allowed us to control for ongoing HR changes during the task, in particular, for those coupled with the respiratory cycle (i.e., RSA). We thus considered 750 ms after the R-peak for an instantaneous HR less than 69.76 bpm; 600 ms after the R-peak for an instantaneous HR between 69.75 and 94.25 bpm; and 400 ms after the R-peak for an instantaneous HR higher than 94.25 bpm (Fittipaldi et al., 2020; García-Cordero et al., 2017; Yoris et al., 2017). A response was considered accurate if it fell within the defined temporal windows. The interoceptive accuracy index was calculated with the formula:

$$1 - (\text{Recorded heartbeats} - \sum \text{Correct Answers}) / \text{Recorded heartbeats}$$

The interoceptive accuracy score range falls between 0 and 1, and higher scores indicate better interoceptive performance.

In the EC, we calculated the exteroceptive accuracy index by time-locking each tapped response with the corresponding time window for each presented heartbeat sound. A tapped response was considered correct if it fell between 0 to 750 ms from the recorded heartbeat (Fittipaldi et al., 2020; García-Cordero et al., 2017; Yoris et al., 2017). As for the interoceptive score, the exteroceptive accuracy index was calculated with:

$$1 - (\text{Heartbeats sounds} - \sum \text{Correct Answers}) / \text{Heartbeat sounds}$$

Mean latencies were also calculated as the average time between every correct tapped response and its corresponding recorded heartbeat (IC) and heartbeat sound (EC). Finally, both IC and EC tapped responses were assigned to "inhale" if the respective R-peak fell within the inhale onset/inhale offset time range and to "exhale" if the R-peak fell within the exhale onset/exhale offset time range. Using the same procedures described above, we calculated interoceptive and exteroceptive accuracy scores and mean latencies corresponding to the inhale and exhale phase of respiration (e.g., "interoceptive accuracy-inhale", "interoceptive accuracy-exhale", "exteroceptive accuracy-inhale", "exteroceptive accuracy-exhale", etc.). An overview of the experimental procedure and data analysis is presented in Fig. 1. We tested for

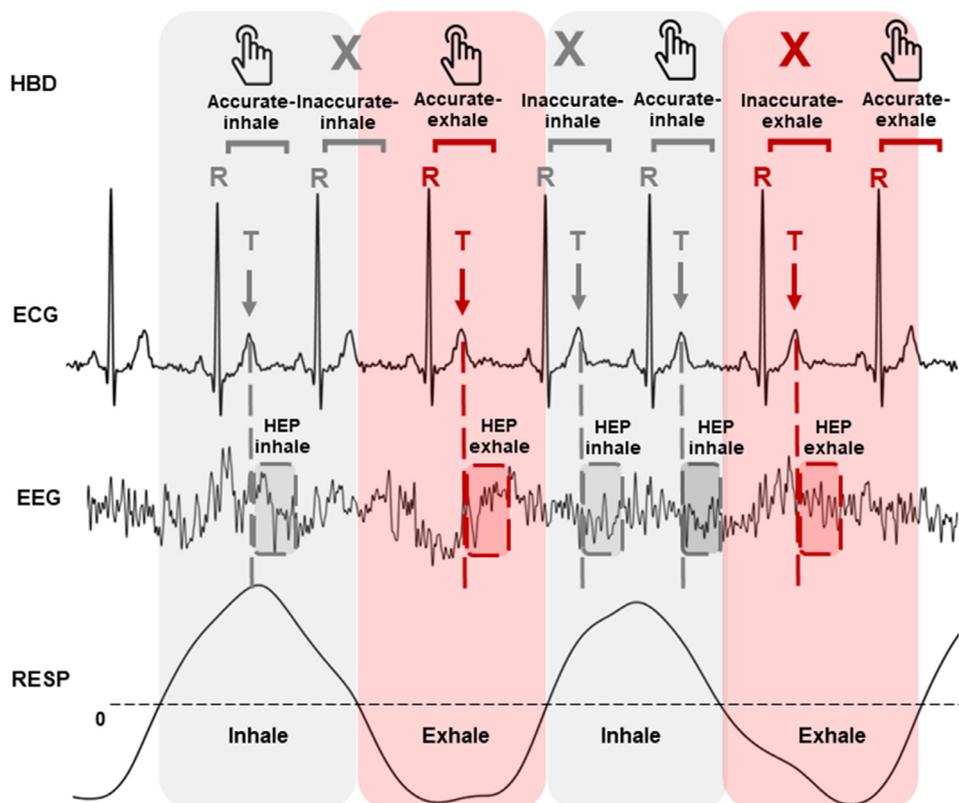


Fig. 1. Schematic representation of data analysis. Grey areas represent inhale phases, pink areas represent exhale phases. The zero-crossing points correspond to the inhale (ascending trace) and the exhale (descending trace) onsets. The HBD row refers to the performance at the Heartbeat Detection task. "Hand" icons represent correct tapped responses. "X" icons represent inaccurate responses. The ECG row represents an exemplary trace of the electrocardiogram. Correct tapped responses were defined as the responses occurring within a given time window time-locked to the previous R-peak of the ECG signal. The width of the time window was individualized, based on the heart rate of each participant. The EEG (electroencephalogram) row represents an exemplary trace of one EEG channel. EEG data were epoched and time-locked to the T-peak (epoch length: -100 to 350 ms). Grey and red squares superimposed on the EEG trace represent the time window where HEP was analysed. We analysed HEP epochs occurring either during inhalation or exhalation, excluding those across respiratory phases. RESP row represents an exemplary trace of the respiratory activity.

changes in task accuracy and mean latencies among respiratory phases (inhale vs. exhale) with a bootstrapped paired t-test (2000 permutations) within both the EC and the IC of the HBD task. Then, to investigate possible interaction effects of task by respiratory phase on task accuracy, we performed a two-way repeated-measures ANOVA on task accuracy with task condition (exteroceptive vs. interoceptive) and respiratory phase (inhale vs. exhale) as within-participants factors.

2.4.5. HEP amplitude statistical analysis

HEP differences between respiratory phases were statistically assessed as in Study 1, for both IC and EC.

Then, to directly compare respiratory phase-induced modulations of HEP (Δ HEP) between the IC and EC, we looked for an interaction effect of task and respiratory phase on mean HEP amplitude by performing a two-way repeated-measures ANOVA with mean HEP amplitude as dependent variable, and task condition (exteroceptive vs. interoceptive) and respiratory phase (inhale vs. exhale) as within-participants factors.

To relate respiratory phase-dependent HEP changes to interoceptive accuracy, we calculated both the participants' Δ HEP index (by subtracting the mean HEP during inhale from the mean HEP during exhale in the significant time-window and electrodes, as in Study 1) and participants' Δ accuracy index (i.e., interoceptive accuracy differences between respiratory phases: "interoceptive accuracy-exhale" minus "interoceptive accuracy-inhale"). Then, based on previous evidence (Katkin et al., 1991; Mai et al., 2018; Montoya et al., 1993; Pollatos and Schandry, 2004; Schandry and Montoya, 1996), we tested the linear positive relationship between participants' Δ accuracy and Δ HEP using Pearson's correlation. One bivariate extreme outlier lying outside the 3rd quartile plus 3*interquartile range was identified by computing Cook's distance and removed from further correlation analyses.

2.4.6. Additional analyses during the heartbeat detection task

2.4.6.1. Task-dependent modulations of neurophysiological variables, regardless of the respiratory phases. Since HEP amplitude has been reported to increase during an interoceptive task (e.g., García-Cordero et al., 2017; Petzschner et al., 2019), we first searched for higher HEP activity during IC compared to EC, regardless of the respiratory phase (See Supplementary Material 9). Second, to investigate whether cardiac and respiratory physiology differed between the two different task conditions under study (IC and EC), we tested for both differences in the ECG signal (averaged within the significant time window of respiratory phase-related HEP effects, as in Study 1), and differences in cardiorespiratory features between the EC and IC using FDR-corrected paired t-tests.

2.4.6.2. Contributions of cardiac and respiratory physiology to respiratory phase-dependent modulations of HEP and accuracy. Within the IC, possible contributions of cardiac and respiratory physiology to HEP and accuracy modulation among respiratory phases were investigated by performing additional analyses both at the subject level (e.g., accuracy, HRV etc.) and at the single-trial level (when possible, e.g., instantaneous HR, ECG signal, and HEP activity).

At the subject level, we tested for any relationship between cardiac activity and HEP changes across participants using Pearson's correlation analyses relating mean HEP changes among respiratory phases (Δ HEP) to a set of cardiorespiratory features of interest (Supplementary Material 1). Since interoceptive accuracy scores increases during exhalations can be highly dependent on concurrent changes in the HR (Ring et al., 1994; Zamariola et al., 2018; Larsson et al., 2021), we first tested whether individual differences in interoceptive accuracy changes among respiratory phases (Δ accuracy) observed during

the IC correlated with changes in HR among respiratory phases, as assessed with HFlog power (an index of RSA). The confounding effect of ongoing changes in HR across respiratory phases was assessed by means of a partial Pearson's correlation analysis, testing the correlation between Δ HEP and Δ accuracy after removing the effects of HFlog power.

At the single-trial level, we tested the effects of the respiratory phase on HEP activity during IC by controlling for HR and ECG activity with a linear mixed-effect model analysis (Supplementary Material 11).

Throughout the manuscript, p-values were adjusted for multiple testing using Benjamini and Yekutieli procedure (FDR, Benjamini and Yekutieli, 2001). FDR threshold was set at $p = 0.05$. Effect sizes were estimated by computing Cohen's d and partial eta squared (η^2p) indices. All statistical analyses were performed in jamovi (v2.2.2; The jamovi project, 2021).

3. Results

3.1. Study 1 – resting-state condition

3.1.1. Overview

We characterized respiratory phase-dependent HEP activity changes by comparing HEP activity between inhalation and exhalation during a 10-minute resting-state condition. We used a comprehensive approach that included the entire EEG sensor space and epoch time window (Petzschner et al., 2019). The homogeneity of the inhale and the exhale phases in terms of number of registered heartbeats and analysed epochs was first verified by performing between-phases paired t-test comparisons (Supplementary Material 5).

3.1.2. Heartbeat-evoked potentials activity among respiratory phases at rest

We determined whether a HEP occurred during inhale or exhale. We then performed a cluster-based permutation t-test to compare HEPs occurred over the whole scalp during the two respiratory phases, between 80 and 350 ms following the T-peak. In a time window ranging from 191 to 350 ms after the T-peak, HEP showed increased positivity, during exhalation, in a wide cluster of frontal, central, and parietal electrodes (FC1, FC2, Cz, C1, C2, C3, C4, CPz, CP1, CP2, CP3, CP4, Pz, P1, P3, POz), peaking on CPz (cluster-based permutation t-test, 10000 permutations, $t(38) = 4.68$, $p_{\text{corrected}} = 0.0022$, Cohen's $d = 0.75$) (Fig. 2A-B). Source reconstruction analysis with sLORETA showed that HEP amplitude was significantly different between the two respiratory phases in two postero-central cortical areas, one on the left hemisphere (cluster-based permutation t-test, 1000 permutations, $p_{\text{corrected}} = 0.002$, cluster statistic (maxsum) = 14061, cluster size = 4093), while the other on the right hemisphere (cluster-based permutation t-test, 1000 permutations, $p_{\text{corrected}} = 0.002$, cluster statistic (maxsum) = 11958, cluster size = 3616). Such respiratory phase-dependent changes of HEP activity mapped onto areas of the Sensorimotor Network (bilateral post-central, paracentral, and pre-central gyrus) and the Default Mode Network (left inferior parietal lobule, and bilateral precuneus, cuneus, intraparietal sulcus, parieto-occipital cortex, and parietal superior lobule) (Fig. 2C).

In line with the T-peak-related HEP results, we found significant exhalation-related HEP increases also when time-locking the HEP to the ECG R-peak, in a time window ranging from 332 to 379 ms after the R-peak. HEP activity showed increased negative amplitude, during exhalation, over a set of frontal and prefrontal electrodes (Fp1, Fp2, Fp7, AF7, AF3, AFz, AF4, AF8, and Fz), peaking on AF3 (cluster-based permutation t-test, 10000 permutations, $t(38) = 2.69$, $p_{\text{corrected}} = 0.01$, Cohen's $d = 0.431$) (See Supplementary Material 3, Supplementary Fig. 2).

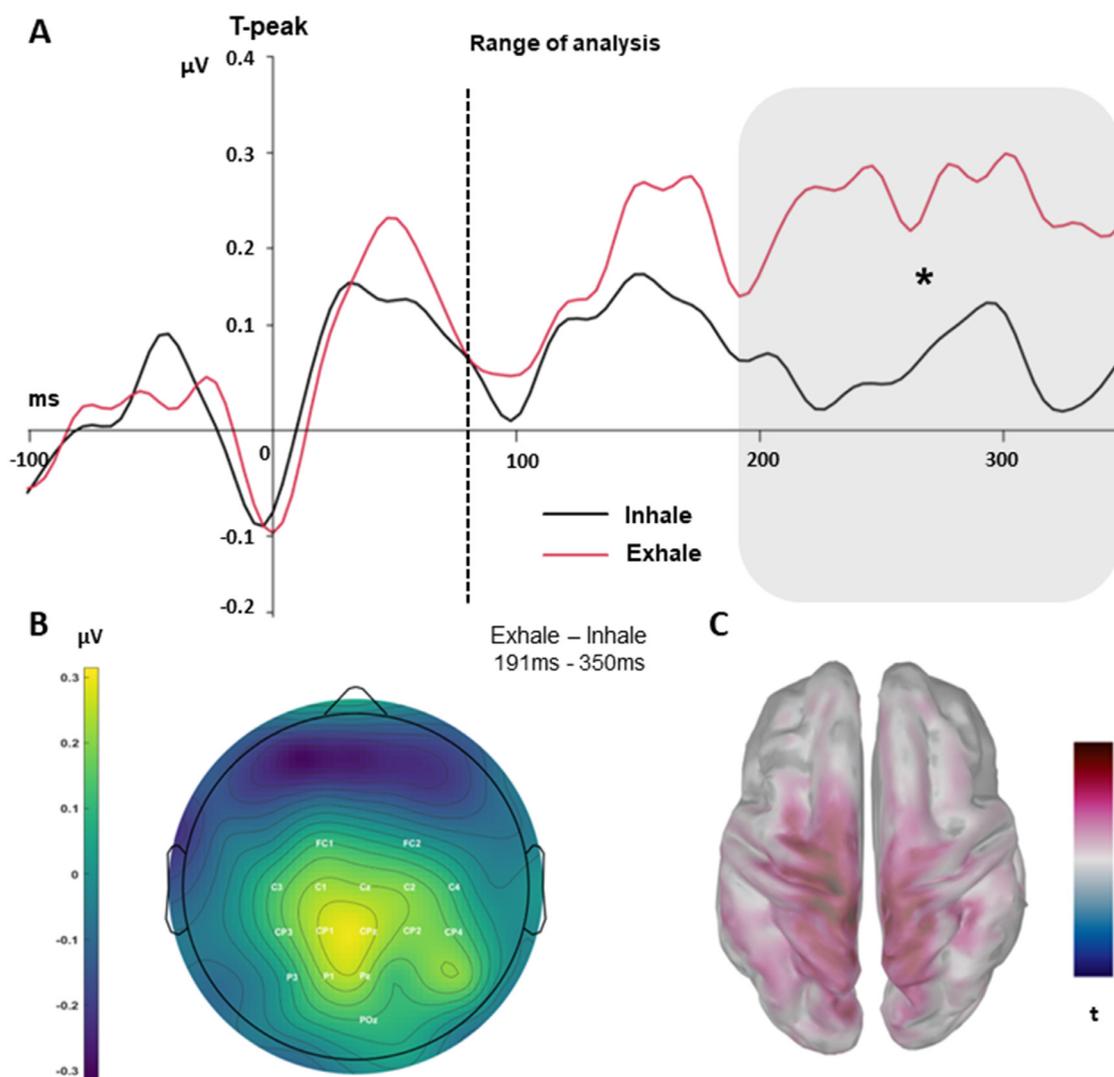


Fig. 2. HEP activity changes among respiratory phases at rest. (A) Grand-average HEP waveforms pooled for significant electrodes. HEP waveform occurring at inhale is indicated in black, HEP waveform occurring at exhale is indicated in red. The dotted lines represent the temporal window of interest used for the statistical analysis (80–350 ms after the T-peak) of the HEP components. The grey rectangle marks the time window of significant differences (191–350 ms after the T-peak) (cluster-based permutation test). (B) Topographical scalp distribution showing the contrast between significant mean HEP differences (191–350 ms after the T-peak) between the exhale and inhale phases. (C) sLORETA source-reconstruction of significant HEP amplitude changes between the exhale and inhale phases in the Sensorimotor Network and the Default Mode Network (cluster-based permutation test).

3.1.3. Additional cardiorespiratory analyses during resting-state

Heart physiology significantly differs between inhalation and exhalation (Draghici and Taylor, 2016; Riganello et al., 2018; Shaffer et al., 2014; Shaffer and Venner, 2013). Hence, its possible confounding influence on HEP activity needs to be checked and ruled out in our study. Therefore, we performed additional analyses to support the assumption that observed differences in HEP amplitude between inhalation and exhalation were not driven by heart stroke volume modifications between phases, indexed by HR and ECG signal amplitude (Buot et al., 2021).

At the subject level, we first looked for the well-known RSA effect on HR. We found, as expected, higher HR during inhalation compared to exhalation (paired t-test, $t(38) = 5.04$, $p < 0.001$, Cohen's $d = 0.808$). Then, we tested for differences in ECG amplitude across the two phases with a repeated-measures two-tailed t-test at all time points within the time window of significant HEP differences, followed by FDR correction for multiple comparisons. We found statistically significant differences between inhale and exhale in ECG amplitude, characterized by increased ECG negativity in the exhale phase (paired t-test, $t(38) = -5.44$, $p_{FDR} < 0.001$, Cohen's $d = 0.87$) (Supplementary Fig. 3). These results suggest

that the heartbeat itself was different during exhalations compared to inhalations.

Then, we performed a correlation analysis testing for any relationship between the observed mean HEP differences among respiratory phases (Δ HEP) and different cardiorespiratory features of interest (Supplementary Table 1). Specifically, we measured the mean HR, HFlog power, HRV total power, and LF/HF ratio as cardiac features, and breathing rate, inhale duration, exhale duration, and I/E ratio as respiratory features. None of these features related to cardiac and respiratory physiology were significantly related to the observed HEP effects (Supplementary Material 6).

At the trial level, to further explore the predictive role of the respiratory phase on HEP activity, while controlling for HR and ECG signal changes, we performed a linear mixed-model analysis evaluating the following parameters on a trial-by-trial basis (14605 trials, clustered around 39 participants): respiratory phase (Phase: inhale vs. exhale), instantaneous HR, single-trial ECG voltage, and single-trial HEP voltage (Supplementary Material 4, Supplementary Table 2, Supplementary Fig. 4). The final model showed a significant main effect of the respira-

tory phase ($b = -0.05476$, $SE = 0.02195$, $t = -2.49$, $p = 0.013$) confirming that respiratory phase-related HEP modulation remains significant when HR and ECG activity are taken into account. The main effects of the intercept ($b = 0.08091$, $SE = 0.08091$, $t = 4.08$, $p < 0.001$) and the HR ($b = -0.00324$, $SE = 0.00143$, $t = -2.26$, $p = 0.025$) were also significant. Finally, we found a significant interaction between Phase and HR ($b = 0.00367$, $SE = 0.00185$, $t = 1.98$, $p = 0.047$) on HEP amplitude, suggesting that respiratory phase-related HEP effects during resting-state are moderated by HR: for each trial, the higher the HR, the lower HEP activity registered during exhalations (Supplementary Material 4, Supplementary Table 2, Supplementary Fig. 4).

3.2. Study 2 – heartbeat detection task

3.2.1. Overview

We tested HEP activity changes across the respiratory cycle in participants performing the IC and the EC of the HBD task. During EC, participants heard a digital heartbeat sound and had to tap a button with their dominant hand in synchrony with it. During IC, they were asked to focus their attention on their own heart and tap a button at each heartbeat. As in Study 1, we verified the homogeneity of the inhale and the exhale phases in terms of number of registered heartbeats and analysed epochs by performing between-phases paired t-tests, both within the EC and the IC of the HBD task (Supplementary Material 7).

3.2.2. Heartbeat-evoked potential changes across the respiratory cycle during IC

We first tested our hypothesis that HEP activity is modulated by respiratory phases during IC. As in Study 1, we first discriminated between HEP occurred during inhale and exhale. Then, we performed a cluster-based permutation t-test comparing HEP occurring during the two respiratory phases, between 80 and 350 ms after the T-peak over the whole scalp. The results showed that during a time window ranging from 234 to 312 ms following the T-peak, HEP increased in positivity in a cluster of central and frontal electrodes (F2, F4, FC2, FC4, Cz, C1, C2, C4, CPz, CP2), peaking on CPz and FC2. This result suggests that cortical processing of the heartbeat increases during exhalation phase, compared to inhalation phase, when participants focused their attention on heartbeats (cluster-based permutation t-test, 10000 permutations, $t(18) = 4.84$, $p_{\text{corrected}} = 0.0236$, Cohen's $d = 1.11$) (Fig. 3A-B, IC).

Second, we tested whether similar HEP modulations among respiratory phases were present also during the EC. To this aim, we compared HEP activity during exhalation and inhalation phases of respiration in participants performing the EC. We adopted two different approaches: first, we compared inhale and exhale HEP over the whole scalp and in the whole time window (80-350 ms), as in IC; second, we focused on space regions of the main respiratory effects previously detected within the IC (i.e., F2, F4, FC2, FC4, Cz, C1, C2, C4, CPz, CP2), in the significant time-window (234 to 312 ms). In both cases, cluster-based per-

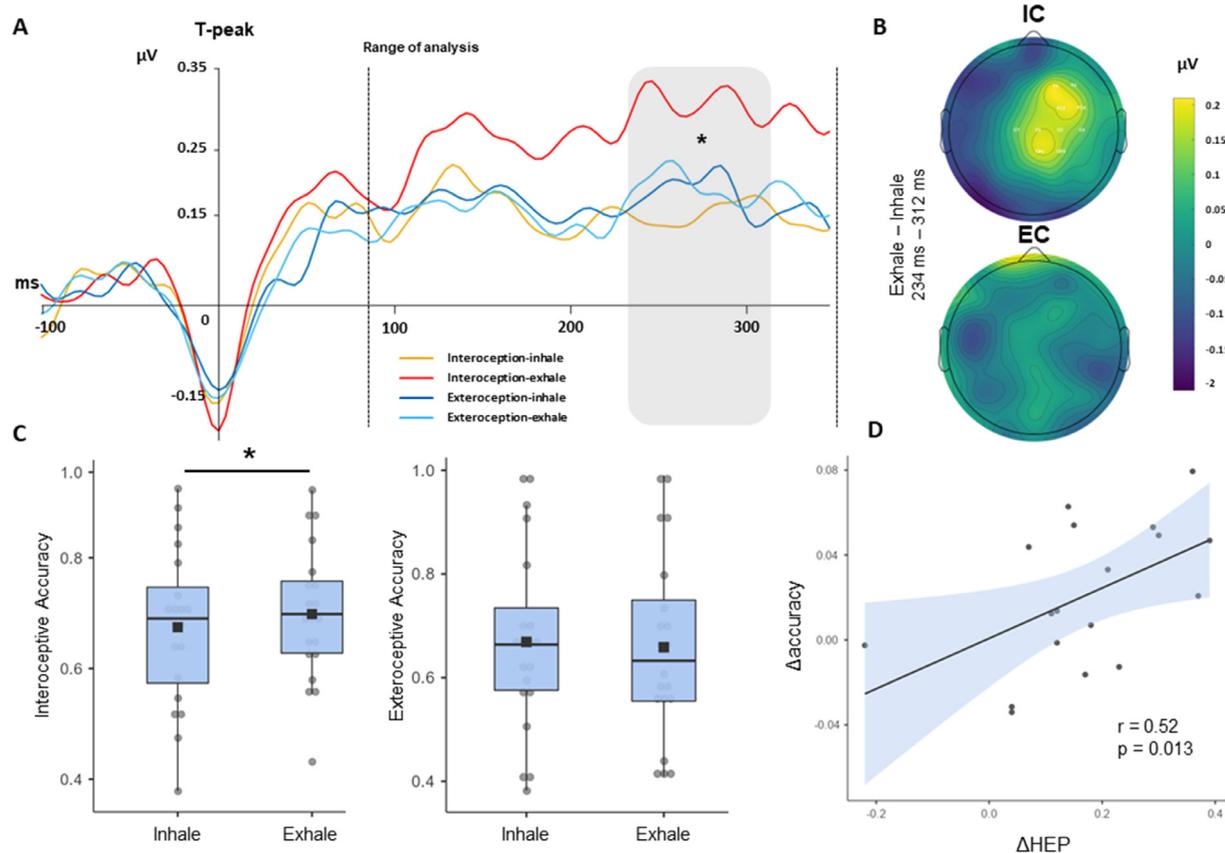


Fig. 3. HEP activity and interoceptive accuracy change across the respiratory cycle during the HBD task. (A) Grand average HEP waveform pooled for significant electrodes. The time courses of the HEP are shown for “Interception-exhale” (red), “Interception-inhale” (orange), “Exteroception-exhale” (light blue), and “Exteroception-inhale” (dark blue). The dotted lines represent the temporal window of interest used for the statistical analysis (80-350 ms after the T-peak) of the HEP components. The grey rectangle marks the time window of significant differences (234 to 312 ms after the T-peak) (cluster-based permutation test). (B) Topographical scalp distribution (234 to 312 ms after the T-peak) shows the difference between the exhale and inhale phases for both the Interceptive Condition (up) and the Exteroceptive Condition (down) of the HBD task. (C) Interoceptive (left) and Exteroceptive (right) accuracy scores of the HBD task for tapped responses plotted against the respiratory phases. The * represents significant differences between interoceptive accuracy scores at inhale and exhale (paired t-test). (D) Scatter plot of the linear relationship (Pearson’s correlation, one tail) between the mean HEP amplitude changes (Δ HEP) and interoceptive accuracy changes (Δ accuracy) among respiratory phases.

mutation t-tests revealed no differences in any cortical cluster (cluster-based permutation t-test, 10000 permutations, $p_{\text{corrected}} > 0.05$, Cohen's $d = 0.0397$) (Fig. 3A-B, EC). This null effect during EC suggests that respiratory phase-dependent HEP changes observed during IC are specifically associated to the direction of top-down attention: towards one's own heartbeat (IC) rather than an external digital heartbeat (EC).

To directly compare respiratory phase-induced changes in HEP (ΔHEP) between the IC and EC, we performed a two-way repeated-measures ANOVA with mean HEP amplitude as dependent variable, while task condition (exteroceptive vs. interoceptive) and respiratory phase (inhale vs. exhale) were the within-participants factors. The ANOVA did not show a main effect of task ($F(1, 18) = 0.229$, $p = 0.638$, $\eta^2p = 0.013$). Differently, the main effect of respiratory phase ($F(1, 18) = 7.782$, $p = 0.012$, $\eta^2p = 0.302$) was significant, indicating increased HEP during exhalation. Most importantly, also the task by respiratory phase interaction was significant ($F(1, 18) = 7.301$, $p = 0.015$, $\eta^2p = 0.289$). This result was explained by stronger respiratory phase-dependent modulation of HEP when top-down attention is directed towards the heart than towards the external heartbeat-like sounds.

3.2.3. Interoceptive accuracy changes across the respiratory cycle

We hypothesized that, along with HEP activity, interoceptive accuracy is specifically modulated by respiratory phases. Therefore, we tested if accuracy of tapped responses given during IC, but not during EC, in the exhale phase of respiration was different from accuracy of tapped responses given in the inhale phase of the same task condition. First, we calculated participants' interoceptive and exteroceptive accuracy and mean latency (Supplementary Material 8). Then, we separately analysed interoceptive and exteroceptive accuracy scores and mean latencies associated to the inhale and exhale phases of respiration. Mean interoceptive accuracy was 69.84 ± 12.56 % [mean \pm SD] for the exhale phase, and 67.45 ± 14.71 % [mean \pm SD] for the inhale phase. In line with HEP findings, a bootstrapped paired t-test (2000 permutations) revealed significant changes in interoceptive accuracy among respiratory phases, indicating increased heartbeat detection during exhalations (paired t-test, $t(19) = 3.14$, $p = 0.005$, Cohen's $d = 0.702$) (Fig. 3C - IC). Mean latency for accurate responses was the same among respiratory phases, being 335.11 ± 36.77 ms [mean \pm SD] for the inhale phase, and 336.68 ± 41.20 ms [mean \pm SD] for the exhale phase (paired t-test, $t(19) = 0.438$, $p = 0.67$, Cohen's $d = 0.0979$).

To test the hypothesis that differences in accuracy among respiratory phases were specific to IC, we similarly calculated accuracy for EC during exhale and compared it to accuracy in the inhale phase of respiration. Mean exteroceptive accuracy was 64.10 ± 16.98 % [mean \pm SD] for the exhale phase, and 65.23 ± 16.94 % [mean \pm SD] for the inhale phase. We did not find any significant modulation of exteroceptive accuracy due to respiratory phases during EC (paired t-test, $t(19) = 1.35$, $p = 0.193$, Cohen's $d = 0.3019$) (Fig. 3C - EC). This result suggests that respiration does not affect the EC of the HBD task. As for IC, mean latency for accurate responses did not change significantly among respiratory phases, being 194.81 ± 66.32 ms [mean \pm SD] for the inhale phase, and 200.64 ± 74.27 ms [mean \pm SD] for the exhale phase (paired t-test, $t(19) = -0.682$, $p = 0.50$, Cohen's $d = 0.1524$).

Next, we performed a two-way repeated-measures ANOVA with task accuracy as dependent variable, while task condition (exteroceptive vs. interoceptive) and respiratory phase (inhale vs. exhale) were the within-participants factors. The ANOVA showed no significant main effect of respiratory phase ($F(1, 19) = 2.808$, $p = 0.11$, $\eta^2p = 0.129$), nor of task condition ($F(1, 19) = 0.189$, $p = 0.669$, $\eta^2p = 0.01$). However, the interaction task by respiratory phase was significant ($F(1, 19) = 6.843$, $p = 0.017$, $\eta^2p = 0.265$). Crucially, this result confirms that, as for HEP activity, respiratory phase-dependent modulations of accuracy are specific to the interoceptive condition.

Most interestingly, in agreement with existing evidence that HEP activity is positively associated to accuracy in heartbeat detection (Canales-Johnson et al., 2015; Marshall et al., 2017;

Pollatos et al., 2005), and according to our hypothesis that such positive association may reflect also consistent modulation of HEP and interoceptive accuracy by respiratory phases, we found significant correlation between interoceptive accuracy changes ($\Delta\text{accuracy}$) and changes of HEP mean amplitude (ΔHEP) (Pearson's correlation, $r = 0.520$, $p = 0.013$, one tail): the stronger the respiratory phase-dependent modulation of HEP activity, the stronger the respiratory-dependent modulation of interoceptive accuracy in individuals performing IC (Fig. 3D).

3.2.4. Additional analyses during the heartbeat detection task

3.2.4.1. Task-dependent modulation of neurophysiological variables, regardless of the respiratory phase.

Since HEP amplitude has been reported to increase during an interoceptive task (e.g., García-Cordero et al., 2017; Petzschner et al., 2019), we searched for increased HEP activity during IC compared to EC, regardless of the respiratory phase. We found increased HEP activity during IC over centro-parietal electrodes (CP1, CP2, P1, P2, and CPz) between 190 to 312 ms after the T-peak (peaking on CP2) (See Supplementary Material 9, Supplementary Fig. 5).

In order to determine if the observed respiratory phase-related HEP modulations during IC were dependent on differences in heart activity between IC and EC, we tested for differences in ECG amplitude across conditions with a repeated-measures two-tailed t-tests at all time points within the time window of significant HEP differences followed by FDR correction for multiple comparisons. We did not find differences between IC and EC in the ECG signals (paired t-test, $t(18) = -0.363$, $p_{\text{FDR}} = 0.721$, Cohen's $d = 0.0834$) (Supplementary Fig. 8). We then compared participants' cardiorespiratory features of interest during the EC and the IC of the HBD task (Supplementary Table 3) with a bootstrapped paired t-test (2000 permutations). Participants had lower breathing rate during the IC, compared to EC (breathing rate: $t(19) = -3.93$, uncorrected $p = 0.001$, $p_{\text{FDR}} = 0.022$, Cohen's $d = 0.84$; inhale duration: $t(19) = 3.51$, uncorrected $p = 0.002$, $p_{\text{FDR}} = 0.022$, Cohen's $d = 0.7$; exhale duration: $t(19) = 3.03$, uncorrected $p = 0.006$, $p_{\text{FDR}} = 0.043$, Cohen's $d = 0.6$).

Whether these changes were due to the different arousing nature of the two conditions, or to spontaneous adjustments of respiration to improve heartbeat perception, cannot be determined based on present data. However, differences in breathing rate across IC and EC were not associated to observed respiratory phase-dependent modulations of HEP during IC (Supplementary Material 10). No other cardiorespiratory feature (HR, HFlog power, HRV total power, LF/HF ratio, I/E ratio) significantly differed between IC and EC (Supplementary Table 3).

3.2.4.2. Contributions of cardiac and respiratory physiology to respiratory phase-dependent modulations of HEP.

Within the IC, we tested if heart physiology differed among respiratory phases (inhale vs. exhale) at the subject level. As for Study 1, we found statistically significant differences between inhale and exhale for HR and ECG amplitude, characterized by increased HR during inhalation (paired t-test, $t(18) = 2.35$, $p = 0.031$, Cohen's $d = 0.539$), and increased ECG negativity in the exhale phase (paired t-test, $t(18) = -5.361$, $p_{\text{FDR}} < 0.001$, Cohen's $d = 1.23$) (Supplementary Fig. 9), which reflects physiological differences in stroke volume across the respiratory cycle (Buot et al., 2021).

Likewise in Study 1, at the subject level we performed a series of correlation analyses during IC, testing for relationships between mean HEP differences (ΔHEP) and cardiorespiratory features (Supplementary Material 12), finding null results. Taken together, all the above-mentioned analyses suggest that observed differences in HEP activity among respiratory phases during IC cannot be simply explained by differences at the level of cardiac physiology.

To deeply investigate the predictive role of the respiratory phase on HEP activity, while controlling for HR and ECG signal changes, we performed a linear mixed-model analysis at the single-trial level assessing respiratory phase (Phase: inhale vs. exhale), and trial-based HR, ECG,

and HEP, as done in Study 1 (7638 trials, clustered around 19 participants) (See Supplementary Material 11, Supplementary Table 4, Supplementary Fig. 6). The final model confirmed a main effect of the respiratory phase ($b = -0.06065$, $SE = 0.02753$, $t = -2.2$, $p = 0.028$), as well as of the intercept ($b = 0.007395$, $SE = 0.0321$, $t = 2.3$, $p = 0.0036$), and of HR ($b = -0.00554$, $SE = 0.00207$, $t = -2.67$, $p = 0.009$) on HEP amplitude. Notably, no interaction effects were found between HR and Phase suggesting that, during IC, HR does not moderate the effect of respiratory phase on HEP activity.

3.2.4.3. Contributions of cardiac and respiratory physiology to respiratory phase-dependent modulations of accuracy. Interoceptive accuracy increase during exhalations can be highly dependent on other factors than cardiac interoception, such as the HR (Ring et al., 1994; Zamariola et al., 2018; Larsson et al., 2021). Thus, we first tested whether individual differences in interoceptive accuracy changes among respiratory phases (Δ accuracy) observed during the IC correlated with changes in HR among respiratory phases, as assessed with HFlog power (a measure of RSA). We found a positive correlation between Δ accuracy and HFlog power (Pearson's correlation HFlog power, $r = 0.541$, $p = 0.02$). That is, the higher the RSA, the higher the detection score increases during exhalation than inhalation at the IC of the HBD task (See Supplementary Fig. 7).

Therefore, to check if the linear relationship between Δ HEP and Δ accuracy was mediated by ongoing HR changes across the respiratory cycle (i.e., RSA), we performed a partial Pearson's correlation analysis relating Δ accuracy and Δ HEP, while controlling for HFlog power. The results revealed that this relationship was not fully explained by RSA (partial Pearson's correlation controlling for HFlog power, $r = 0.447$, $p = 0.036$, one tail), suggesting that accuracy changes were not entirely mediated by RSA, but were associated to cardiac interoception.

4. Discussion

4.1. Overview

The fundamental influence of respiration on brain activity and cognitive functions in humans has been increasingly recognized in the last few years (Heck et al., 2017; Kluger and Gross, 2021; Varga and Heck, 2017). However, its potential role in fine-tuning brain-heart interactions has gone mostly unstudied within the interoception research field so far. In the present work, we performed two studies with the general aim of investigating the role of spontaneous respiration in shaping the cortical processing of cardiac-related information. In both studies, we focused on HEP activity modulations, an EEG event-related potential time-locked to the ECG signal, commonly regarded as an objective electrophysiological index of brain-heart interactions (Coll et al., 2020; Park and Blanke, 2019a).

4.2. Neuro-cardio-respiratory interactions at rest

Our first specific aim was to investigate the interplay between the cardiac, respiratory and brain activity in a resting-state condition, that is, while participants were let mind-wander and spontaneously breathe. Hence, in Study 1, we recruited healthy volunteers and computed HEP levels separately for heartbeats occurred during the inhalation and the exhalation phases of the respiratory cycle. We found higher HEP amplitude during exhalation compared to inhalation, indicating increased brain-heart interactions and improved cortical processing of the heartbeats. HEP levels significantly increased in a time window ranging from 190 to 350 ms after the T-peak over frontal, central, and parietal electrodes, and peaked on CPz. Source-level respiratory effects on HEP were localized in cortical regions overlapping the Sensorimotor Network and the Default Mode Network. Specifically, they included the left inferior parietal lobule, the bilateral post-central, paracentral, and pre-central

gyri, the precuneus, cuneus, intraparietal sulcus, superior parietal lobule, and parieto-occipital cortex. These results are consistent with previous evidence showing higher HEP activity over medial posterior areas associated to self-related processes during mind-wandering (Babo-Rebello et al., 2016).

A first interpretation of the present results may refer to the strong coupling between the respiratory cycle and the baroreflex. This well-known interaction is commonly referred to as RSA, a form of cardiorespiratory synchronization resulting in cyclic HR increases during inhalations and subsequent decreases during exhalations (Brecher and Hubay, 1955). RSA is mechanically induced by inhalation-dependent decrease of pleural pressure driven by chest expansion, which facilitates venous return to the right heart. This causes a reduction of the left ventricular stroke volume, decreasing aortic blood pressure, which in turn is sensed by aortic baroreceptors. Lower baroreceptor stimulation during inhalation then triggers the baroreflex: to stabilize cardiac output over the short term, the HR temporarily increases. However, this also means that when HR increases, heartbeats are inherently weaker (Draghici and Taylor, 2016; Riganello et al., 2018; Shaffer et al., 2014; Shaffer and Venner, 2013; Larsson et al., 2021). Regarding the present study, being inhalations associated to increases in HR, they are also inextricably linked to weaker (or less salient) heartbeats, eventually resulting in the observed reduction of the HEP during inhalations compared to exhalations.

To further explore this hypothesis, we performed a series of analyses on both the ECG signal and cardiorespiratory features. Supporting the interpretation that increased HEP levels may result from stronger heartbeats during exhalation, we found both decreased HR and increased amplitude of the ECG signal in the exhalation compared to the inhalation phase. Hence, we tested whether instantaneous HR and ECG signal interacted with the respiratory phase-related effects on HEP at the single-trial level. Results showed that respiratory phase-related HEP effects were significantly moderated by HR changes. However, respiratory phase-related HEP modulations remained significant when HR and ECG activity were taken into account in the model, suggesting that other factors may have come into play.

A complementary interpretation of our results is that afferent interoceptive information travelling from the heart to the cerebral cortex could be also modulated by simultaneous sensorimotor signals generated by pulmonary afferents as well as by the active movement of the chest (see Baumert et al., 2015 for a similar interpretation). Indeed, heartbeat and respiratory interoceptive signals follow similar pathways, as both aortic baroreceptors and rapidly-adapting pulmonary stretch receptors send information about the state of the cardiac and respiratory systems through the vagal nerve and the nucleus of the solitary tract (Park and Blanke, 2019a). It is worth highlighting here that respiratory sensorimotor and interoceptive information is sent upstream primarily during inhalations (Noble and Hochman, 2019; Streeter et al., 2012). Therefore, in this specific respiratory phase, weaker cardiac baroreceptor-mediated information may compete with, and likely lose against, stronger respiratory-mediated information. This would result in increased respiratory sensorimotor interference over cardiac signals, and, possibly, a reduced encoding of cardiac information. Supporting this hypothesis, we found that source-level HEP reduced activity during inhalations, compared to exhalations, was localized over brain regions that have been classically associated to respiratory phase-dependent fMRI modulations, that is, the Sensorimotor Network (Bijsterbosch et al., 2017; Birn et al., 2006; Power et al., 2020).

4.3. Neuro-cardio-respiratory interactions during interoceptive and exteroceptive attentional tasks

Our second specific aim was to explore if the above-described neuro-cardio-respiratory interactions are further modulated by endogenous attention towards interoceptive vs. exteroceptive signals and if this modulation affects individual interoceptive vs. exteroceptive accuracy at be-

havioural level. In Study 2 we simultaneously recorded EEG, ECG, and respiratory activity in healthy volunteers during the IC and the EC of the HBD task (Fittipaldi et al., 2020; García-Cordero et al., 2017; Yoris et al., 2017). We observed significant respiratory phase-dependent modulation of HEP activity exclusively during IC. As in Study 1, HEP activity increased during exhalations in a time window ranging from 234 to 312 ms after the T-peak. This effect was found over a cluster of central and frontal electrodes, peaking at CPz and FC2. During EC, we observed no effects of the respiratory phase on HEP activity, suggesting that when attention is focused on the external environment, heart-brain interactions are no longer modulated by respiratory phases. Similarly, at the behavioural level, we found that the exhalation phase of respiration was beneficial exclusively for interoceptive accuracy, while exteroceptive accuracy was not modulated by respiratory phases. Direct comparisons of respiratory phase-induced modulations of HEP (Δ HEP) and accuracy (Δ accuracy) between the interoceptive and exteroceptive conditions showed specific Δ HEP and higher Δ accuracy during the IC, compared to the EC. Interestingly, these modulations were positively correlated. Notably, differently from Study 1, further analyses showed that during the interoceptive task, proxies of heart stroke volume such as the ECG and the HR did not moderate respiratory phase-related effects on HEP activity, but showed an independent effect of HR over HEP amplitude.

To summarize, Study 2 confirms the findings of Study 1 and further extends them by showing that cortical processing and perception of heartbeats are optimized at exhalation, and that this effect is not moderated by heart stroke volume when attention is directed towards interoceptive signals.

To better understand the results of Study 2, which seem to be unrelated to peripheral effects, we can interpret the role of top-down attention towards the heartbeat during IC and towards the environment during EC within the framework of the predictive coding model of interoceptive perception (Barrett and Simmons, 2015; Seth, 2013; Seth and Friston, 2016). In brief, recent interoceptive inference models (Allen et al., 2019; Allen et al., 2021) posit that cardiorespiratory interoception is able to shape the neural gain (i.e., the balance of neural excitation vs. inhibition) across several brain regions by modulating the computational precision (i.e., the inverse of noise) of perceptual, cognitive, and emotional processes. More in detail, periodic physiological changes related to rhythmic cardiorespiratory oscillations are computed by the brain as stable predictions and are centrally suppressed via a sensory attenuation process in order to minimize their interference. Accordingly, recent studies (Al et al., 2020, 2021; Grund et al., 2022) on heart functions found that the systolic phase of the cardiac cycle (i.e., when baroreceptor activity is at a maximum) was related to simultaneous attenuation of somatosensory perception. This effect was explained by the functional cortical overlapping between somatosensory perception and cardiac interoception, at the level of the primary somatosensory cortices: in these regions, the same sensory attenuation process that minimized systole-related oscillations also reduced somatosensory processing (Al et al., 2020, 2021).

Similarly, we propose that the brain receives recursive and predictable interoceptive signals during inhalations, forming stable predictions about each respiratory cycle, and consequently suppressing the physiological signals associated to it within the Sensorimotor Network (Birn, 2012). Since sensorimotor areas are also involved in heartbeat-related information processing (Park and Blanke, 2019a), cardiac-related sensations of heartbeats occurring during inhalations could be suppressed together with those related to respiration. This would explain the observed decrease of HEP activity during inhalations within this network.

According to the same model, top-down attention would increase the precision of what is relevant for the organism in a specific moment, by modulating neuronal gain that represents the target objects at the expense of others (Feldman and Friston, 2010; Smout et al., 2019; Boyadzhieva and Kayhan, 2021). Then, during IC, the brain may assign

the highest priority to heartbeat signals; on the opposite, during EC, the brain may assign the highest priority to the heard sounds. Notably, however, during both IC and EC the heart stroke volume changes in phase with respiration, and the brain receives recursive, predictable, and higher respiratory-related noise during inhalations than exhalations. Hence, the question arises of why we observed different respiratory phase-dependent modulations of HEP activity between the IC (higher Δ HEP) and the EC (lower Δ HEP). Based on the above-described interoceptive inference models (Allen et al., 2019; Allen et al., 2021), interoceptive prediction is not an all-or-none phenomenon, but a highly context-sensitive process determining the precision of incoming sensations based on the ongoing task-oriented cognition. Therefore, during the IC, to be able to correctly perceive and process heartbeat sensations across the respiratory cycle, the brain may adaptively increase the precision of interoceptive cardiac input specifically during exhalations, that is, when inhalation-related physiological noise is absent. This is not necessary during the EC, because top-down attention likely leads to optimization of perception and processing of auditory signals, which does not require any optimization of heartbeat signal processing. Hence, interoceptive optimization of the heartbeat signal processing across the respiratory cycle may occur specifically during the IC, reflected by higher HEP increases during exhalations (higher Δ HEP), but not during the EC (lower Δ HEP). Notably, this process is not modulated by peripheral cardiac components such as the heart stroke volume (indexed by HR and ECG; Buot et al., 2021), likely being more affected by top-down, interoceptive components of attention. This interpretation is further supported by the linear correlation between respiratory phase-induced modulation of both HEP and interoceptive accuracy, with higher Δ HEP (i.e., interoceptive optimization) associated to higher increase of cardiac interoceptive accuracy (Δ accuracy). This clearly suggests that the Δ HEP index herein reported during an interoceptive task for the first time reflects a degree of optimization of interoceptive processing, via interoceptive attention, that is independent from heart stroke volume and is relevant for interoceptive perception.

4.4. Conclusions and limitations of the study

Overall, present findings reveal a so far unnoticed influence of respiration on cardiac interoception: when contextualized within a breathing organism, cardiac interoception is highly interconnected with the respiratory cycle, in addition to task-oriented cognition. Accordingly, we propose that the respiratory phase-dependent HEP modulation (Δ HEP) could represent a physiological index of cardiac interoceptive optimization, with behavioural implications, above and beyond HEP activity alone. In general, we underline the importance of investigating the synergic interplay between different visceral signals, which have been classically studied in isolation within the field of interoception research (Garfinkel et al., 2016; Criscuolo et al., 2022). In particular, building on the present research, future studies should investigate neuro-cardio-respiratory interactions during different interoceptive and exteroceptive tasks.

In fact, a limitation of the present study is that the occurrence of motor tapped responses during the HBD task made the comparison between Δ HEP during task vs. rest inappropriate, due to motor-related confounding activity intrinsic to the HBD task. In addition, HEP activity measured during the HBD task is likely confounded by the motor activity associated with tapped response, even if directly compared with its exteroceptive (control) condition (but see Salamone et al., 2018, for a control of the motor-evoked potential). To overcome this limitation, future studies could, for instance, adopt the Schandry task (Schandry, 1981), a non-motor-based cardiac interoceptive task, making direct comparisons of Δ HEP during rest and task possible.

Future studies can also test if voluntary breath-control, in particular the slowing down of the breathing frequency or the specific increase of the exhalation duration (i.e., the decrease of the I/E ratio), may modulate neurophysiological and behavioural signatures of cardiac

interoception (MacKinnon et al., 2013). This would be particularly relevant to better understand the relationships between interoception and mental health, because breath-control is a highly recommended practice in a whole range of clinical applications and mind-body interventions (Farb et al., 2015; Paulus, 2013; Weng et al., 2021; Zaccaro et al., 2018, 2022). Finally, the link between Δ HEP and interoception could be tested in different clinical or sub-clinical populations with known altered or reduced interoceptive sensitivity, such as generalized anxiety disorder, major depression, and schizophrenia (Ardizzi et al., 2016; Bonaz et al., 2021).

To conclude, in line with the active sensing interpretation of respiratory activity, we speculate on the existence of a breathing-related attentional “switch” between interoception and exteroception. It is already known that inhalation leads to adaptive modulation of neuronal gain in order to facilitate reception and elaboration of sensory information from the external environment (Grund et al., 2022; Huijbers et al., 2014; Kluger et al., 2021; Perl et al., 2019; Zelano et al., 2016). As inhalation itself improves exteroception-related cognitive functions, exhalation may reflect a more general attentional shift towards the internal bodily states and the self, hence modulating interoceptive perception as well as self-consciousness (Molle and Coste, 2022; Park et al., 2018; Park and Blanke, 2019b). That is, spontaneous breathing may continuously tune the brain to switch from extrinsically (external) oriented processing during inhalation, to intrinsically (internal) oriented functions during exhalation (Golland et al., 2007).

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Credit authorship contribution statement

Andrea Zaccaro: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Visualization, Writing-Original Draft, Writing-Review & Editing. Mauro Gianni Perrucci: Methodology, Software, Data curation, Resources, Writing-Review & Editing. Eleonora Parrotta: Software, Formal analysis, Writing-Review & Editing. Marcello Costantini: Visualization, Supervision, Funding acquisition, Writing-Review & Editing. Francesca Ferri: Conceptualization, Methodology, Resources, Supervision, Project administration, Funding acquisition, Visualization, Writing-Review & Editing.

Data and code availability statement

The code used to analyze the experiment is available in an open repository at the following link: https://github.com/azaccaro90/HEP_respiration.git. The behavioral and physiological raw data can be shared by the corresponding author upon request if data privacy can be guaranteed according to the rules of the European General Data Protection Regulation (EU GDPR). The repository also contains anonymized data of a participant of Study 1 and Study 2.

Declaration of Competing Interest

The authors declare no competing financial interest.

Data Availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.neuroimage.2022.119548](https://doi.org/10.1016/j.neuroimage.2022.119548).

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