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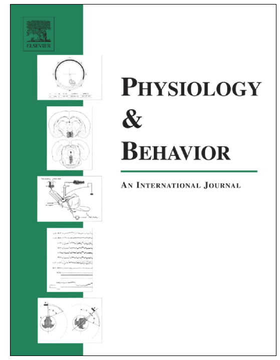

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Mindaugas Baranauskas, Aida Grabauskaitė, Inga Griškova-Bulanova

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Brain responses and Self-Reported Indices of Interoception: Heartbeat Evoked Potentials are inversely associated with Worrying about Body Sensations

Mindaugas Baranauskas[#], Aida Grabauskaitė[#], Inga Griškova-Bulanova*

Institute of Biosciences, Vilnius University, Vilnius, Lithuania

# Equal contribution

*** Corresponding Author**
Inga Griškova-Bulanova
Institute of Biosciences
Vilnius University
Saulėtekio al. 7
LT-10257 Vilnius
Lithuania
Phone: +37067110954, Fax: +37052398204
E-mail: i.griskova@gmail.com, inga.griskova-bulanova@gf.vu.lt

Abstract

Interoception may be defined as a group of senses reflecting physiological state of the body; however the link between physiological and self-reported indices of interoception is not well established. We aimed to elucidate the relationship between the CNS representation of interoceptive processing – the late part of the heartbeat evoked potential (HEP) – and the self-reported interoceptive abilities and tendencies as assessed with the scales of *Multidimensional Assessment of Interoceptive Awareness (MAIA)* questionnaire. The HEP amplitudes at 400-600 ms and MAIA scores from 30 healthy participants were subjected to the cluster-based permutation tests on the t-values of Pearson correlations. HEP amplitudes were positively associated with individual scores on the *Not-Worrying* scale of MAIA at Cz in the time window from 400 ms to 545 ms after the R peak. No other MAIA scales were related to the late HEP amplitudes, suggesting that scales and HEPs measure different aspects that are not directly interrelated. This supports the need to treat interoception as a multidimensional construct.

Keywords: interoception, heartbeat evoked potential, Multidimensional Assessment of Interoceptive Awareness.

Abbreviations: HEP, heartbeat evoked potential; MAIA, Multidimensional Assessment of Interoceptive Awareness; ACC, anterior cingulate cortex

1. Introduction

Interoception may be defined as a group of senses reflecting physiological state of the body. In early studies interoception was strictly referred to the visceroception, however later theories have expanded this concept to the sense of physiological state of the entire body, excluding proprioception [1–7]. Although for decades numerous physiological, behavioral and self-reported indices were used to evaluate various aspects of interoception [8], to date, only a few studies used the indices simultaneously and provided empirical evidence to clearly support multifaceted nature of this sense [9–11]. Overall, there is an increasing need to assess both qualitative and quantitative aspects of interoception, and to investigate the complex relationships between interoceptive indices (see also review [12]).

From the *behavioral indices* of interoception, most frequently used aimed to evaluate *interoceptive accuracy* while detecting bodily signals, for example during the heartbeat counting task, which was developed by Schandry [13], or during the heartbeat discrimination task, which was proposed by Brener and Jones [14] and further elaborated by others (see review [8,12]).

The *self-reported indices* are used to assess qualities of *subjective interoception*, i. e. reflections upon one's autobiographical experiences of interoceptive states, person's beliefs on the aspects of his/her own abilities and tendencies to consciously sense signals originating from the inside of the body, and they are most commonly assessed using questionnaires [7,15]. Though extensively applied, especially in clinically oriented studies, earlier questionnaires were not directly related to the detection of interoceptive sensations *per se* and generally were affected by other perceptual factors [8,16].

An important shortcoming of purely behavioral/self-rated assessment stems from the fact that some modalities of the body sensations are near or below the level of conscious perception. For example, most individuals consciously perceive only a fraction of heartbeats even while paying attention during the cardio-receptive tasks [17–20]. Contrary to the tasks relying on perception of one's heartbeats, brain responses to heartbeats can be detected without direct attention or perception [21], making them a valuable tool to investigate interoception.

One of the currently utilized objective *psychophysiological / neuroimaging indices* to assess CNS representations of visceral-afferent signals related to interoceptive information processing is the *heartbeat evoked potential (HEP)* – an electrical response of the brain that is locked to the heartbeat. HEP amplitudes at around 200–350 ms after the EKG R wave with a peak at the medial-right frontocentral sites have been mostly investigated and interpreted as a CNS representation of sensory information processing related to cardiac *interoceptive accuracy* [22–28]. The later HEP interval around 400–600 ms after the EKG R wave being pronounced at various sites (e. g. [29–32]) is increasingly investigated in relation to various aspects of interoception. Importantly, the late HEP interval is believed to be free of cardiac electromagnetic field and pulsatility artifacts [33,34]. Recent studies have shown that the amplitudes of the late HEP were related to dysregulation of emotions [29], emotional arousal [35], stress-induced changes in cardiac output [36], and were altered in subjects with insomnia disorders [37]. Although earlier works failed to show the relationship between amplitudes in the late HEP interval and interoceptive accuracy [30,31], the abovementioned findings on the late HEP amplitudes suggest that this part of the response could be related to the features of interoception that are assessed by self-reports.

The subjective evaluation of qualitative aspects related to the general interoceptive abilities and tendencies is possible by recently proposed *Multidimensional Assessment of Interoceptive Awareness (MAIA)* [7]. The number of research studies using the MAIA questionnaire is rapidly growing, supporting its validity and acceptable reliability for most of the MAIA scales [38–46]. The broad range of the assessed aspects makes MAIA a valuable tool that could be used to link physiological responses to subjective experiences; however both measures – HEPs and MAIA – have never been assessed in the same sample and related one to the other before. Thus, we aimed to elucidate the relationship between the CNS representation of interoceptive processing – the late part of the heartbeat evoked potential – and self-reported interoceptive abilities and tendencies as assessed with the scales of *Multidimensional Assessment of Interoceptive Awareness* questionnaire. Based on the known associations of the late HEP amplitudes to the number of body sensation- and regulation-related aspects, we hypothesized that individual differences in qualitative aspects of interoception could be reflected in the late HEP amplitudes.

2. Methods

2.1. Participants

The study sample consisted of 40 volunteers (20 males). The mean age of the sample was 24.03 years (SD = 2.43). All the participants met the following inclusion criteria: age between 18 and 30, ability to participate in all of the experimental procedures without having a break, normal or corrected-to-normal visual acuity. Volunteers were in a good general health – had no history of heart activity related disorders and reported no other diagnosed illness; were not taking any medication that might affect mental or physiological processes. Participants reported having more than 6 hours of sleep before the experiment and were not experiencing strong emotions at the time of the experiment. The information was collected in the form of self-reported questionnaire. The study was approved by the Lithuanian Bioethics Committee, and all participants gave their written informed consents. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Procedure

Upon arrival, participants filled out a questionnaire for personal data collection (e. g., age, health status) and the Lithuanian version of the *Multidimensional Assessment of Interoceptive Awareness (MAIA)* [38].

Participants were seated ≈ 0.8 m in front of the LCD screen in an electrically shielded room, where they completed all subsequent tasks. Participants were asked to sit still and fixate at a bright grey cross against a black background on the computer screen for 10 minutes, while psychophysiological data were recorded.

2.3. MAIA questionnaire

The Lithuanian version of MAIA scales was filled in the paper form. Participants were asked to evaluate each of 32 statements on a Likert scale from 0 (never) to 5 (always). MAIA questionnaire is composed of eight scales: *Noticing* – awareness of uncomfortable, comfortable, and neutral body sensations; *Not-Distracting* – tendency not to ignore or distract oneself from sensations of pain or discomfort; *Not-Worrying* – tendency not to worry or experience emotional distress with sensations of pain or discomfort; *Attention Regulation* – ability to sustain and control attention to body sensations; *Emotional Awareness* – awareness of the connection between body sensations and emotional states; *Self-Regulation* – ability to regulate distress by attention to body sensations; *Body Listening* – active listening to the body for insight; *Trusting* – experience of one's body as safe and trustworthy. The score for each scale is counted by averaging the scores of items belonging to each scale (items from 5 to 9 were reversed).

The scores on MAIA scales were compared between sexes using Student t-test. Additionally, to check the independency of MAIA scales in our sample, we performed Pearson correlation analysis (see Supplementary data 1).

2.4. Psychophysiological measurements and analysis

Sixteen EEG electrodes of the WaveGuard EEG Cap were used for EEG recordings: Fp1, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2, M1, M2 placed according to the International

10-20 system. The ground electrode was placed at AFz. The recording reference was Cz. EKG electrodes were placed on the forearms near the wrists. EOG electrodes were used for the detection of horizontal and vertical eye movements. Electrical signals were recorded using *ASALAB* (*ANT Neuro*, the Netherlands) system. Signals were recorded using a 1024 Hz sampling rate.

For the off-line data processing all psychophysiological signals were re-referenced to linked mastoids, FIR band-pass filtered between 0.3 and 30 Hz using *EEGLAB* for *MATLAB* [47]. Later, R peaks in the EKG recording were identified using a modified Pan-Tompkins [48] algorithm and, after visual inspection, event markers for each R peak were added to EKG and EEG. EKG and EEG were further subjected to manual cleaning. Independent component analysis (ICA) was used to identify and remove horizontal and vertical eye movements. Noisy EEG channels were interpolated. HEPs were extracted by creating EEG epochs of 800 ms: from −200 ms to 600 ms relative to the R peaks. Epochs were rejected from the analysis if the voltage exceeded ±50 μV in any of the channels. Only epochs of 750 ms or more from the previous R peak were included in the average. HEPs were baseline-corrected by subtracting the mean of the baseline period (window from −200 ms to −50 ms relative to R peaks).

Following previous research, we analyzed HEPs at the time interval from 400 ms to 600 ms after the R peak. This time-period is thought to be free of cardiac field artifacts and previously was associated to interoception-related processes [29,30,36,49,50].

Mean HEP amplitudes of 12 channels (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2) in 400−600 ms time window relative to the EKG R peak were compared across hemispheres – left (F3, C3, P3, O3) / midline (Fz, Cz, Pz, Oz) / right (F4, C4, P4, O4) – and areas – frontal (F3, Fz, F4) / center (C3, Cz, C4) / parietal (P3, Pz, P4) / occipital (O3, Oz, O4) – with repeated measures ANOVA analysis and sex was included as a between-subject variable. Sphericity assumption was checked with the Mauchly sphericity test and Greenhouse-Geisser adjustment was applied when necessary.

For the evaluation of the relationship between HEP amplitudes and scores of MAIA scales, Pearson correlation analysis was performed. To identify time windows and scalp areas where HEP amplitude significantly correlated with MAIA scores, while correcting for multiple comparisons over the multiple time samples and channel locations, we applied a cluster-based permutation test [51] across the same 12 channels (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2) and 204 time samples from 400–600 ms window after the R peak. The cluster-based permutation test was performed in a "Mass Univariate ERP Toolbox" [52] on the two-tailed t-values of Pearson correlation (the initial code that used Student t-test was changed). All t-scores corresponding to the uncorrected p-values of 0.05 or less were grouped into clusters on the basis of spatial and temporal adjacency. To establish the likelihood that a cluster was obtained by chance, original HEP data were shuffled 20 000 times with respect to the scores on individual MAIA scales (one scale at a time). Remaining parameters for the "Mass Univariate ERP Toolbox" remained at default values. The sum of the t-scores in each cluster is the "mass" of that cluster and the most extreme cluster mass in each of the sets of tests was recorded and used to estimate the distribution of the null hypothesis (i.e., no correlation between HEP amplitudes and scores on MAIA scales). The permutation cluster mass percentile ranking of each cluster from the observed data was used to derive its p-value. In case of significant permutation results, individual mean HEP amplitudes in the identified significant window were correlated to the corresponding individual MAIA scale scores. To control for the potential influence of the heart rate variability (HRV) on the significant correlations, a partial correlation analysis including HRV measures was performed (see Supplementary data 2).

Where appropriate, we applied the Bonferroni correction for multiple comparisons [53].

3. Results

The data of 10 participants were rejected due to the following reasons: one participant had extrasystoles; the data of three participants were highly contaminated by artifacts; the data of 3 participants had relatively high heart rate (R-R interval less than 750 ms, resulting in less than 200 epochs for averaging); the data of 3 participants were rejected due to their mean HEP amplitudes in 400–600 ms time window after the EKG R peak were treated as outliers (defined as less than $Q_1 - 3\times IQR$ or more than $Q_3 + 3\times IQR$). The remaining sample consisted of 30 participants: 14 males and 16 females.

3.1. Heartbeat evoked potential

Mean number of epochs included into the individual average HEP was 444 (SD = 111). The grand-average HEP waveforms and the corresponding averaged EKG waveform are presented in Figure 1A and B.

The mean HEP amplitudes in the 400–600 ms interval were normally distributed (Shapiro-Wilk test; $p \geq 0.049$) at all EEG channels. The grand averaged topography plot of HEP in 400-600 ms window is presented in Figure 1C.

The evaluation of the area (frontal vs central vs parietal vs occipital) and the hemisphere (left vs midline vs right) by 3×4 ANOVA analysis indicated that mean HEP amplitudes in 400–600 ms window differed across anterior-posterior direction ($F(2.32, 67.3) = 8.503$, $p < 0.001$, $\eta^2 = 0.227$). The *post hoc* comparison revealed that amplitudes at the central (M = –0.17, SE = 0.10, p = 0.005) and parietal (M = 0.16, SE = 0.10, p = 0.003) areas were more positive compared to the frontal area (M = 0.30, SE = 0.10). No significant effects of hemisphere (F(2, 58) = 0.270, p = 0.764, $\eta^2 = 0.009$) or interaction between the area and hemisphere factors (F(3.56, 103.1) = 0.837, p = 0.493, $\eta^2 = 0.028$) were observed. The sex factor did not influence the results (F(1,28) = 0.27, p = 0.61) and there were no significant interaction between sex and other factors.

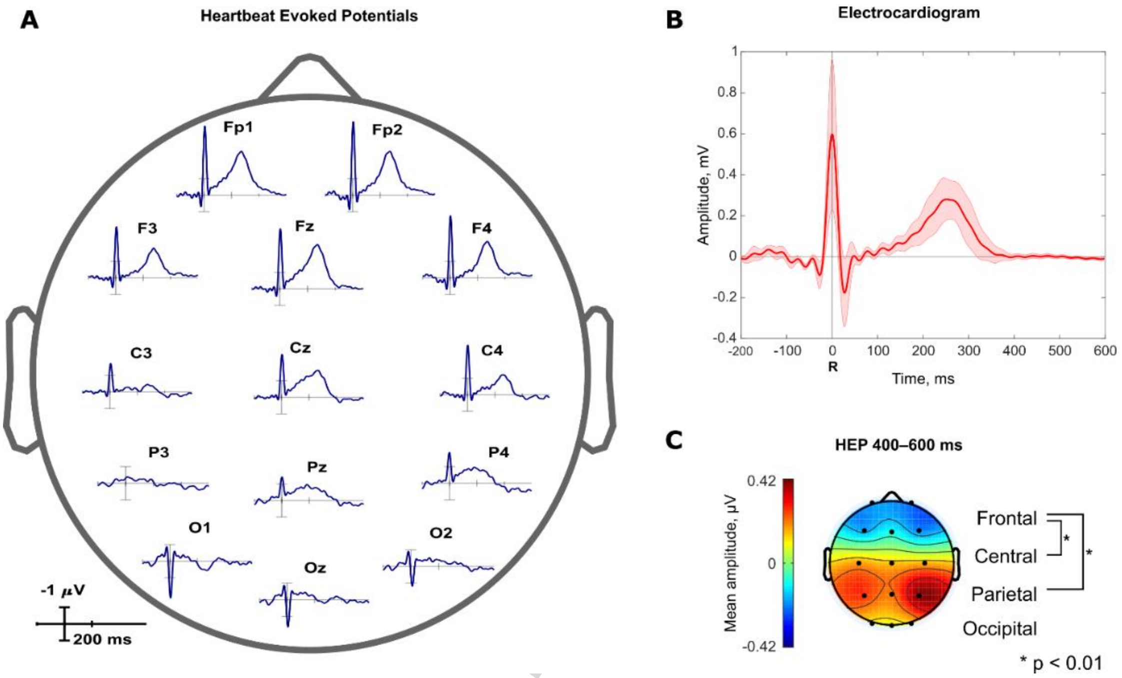

Figure 1. (**A**) Topographical representation of grand-averaged HEP waveforms. (**B**) Grand-average waveform of EKG (shaded area denotes SDs). (**C**) Topographical representation of mean HEP amplitudes in 400–600 ms time window relative to the EKG R peak. The significant differences of amplitudes among frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) areas are marked with *.

3.2. Multidimensional Assessment of Interoceptive Awareness (MAIA)

The scores of all MAIA scales were normally distributed (means and SDs presented in Table 1). No differences were found between sexes for *Noticing, Not-Distracting, Not-Worrying, Attention Regulation, Self-Regulation, Trusting* scales; however females had higher scores on *Emotional Awareness* scale (p = 0.011, M = 3.74 for females, M = 3.06 for males) and on *Body Listening* scale (p = 0.004, M = 2.65 for females, M = 1.64 for males).

Table 1. Means and SDs of the scores on MAIA scales (N = 30). Scales with different scores between sexes are presented in italics.

	Mean	SD
Noticing	3.433	0.639
Not-Distracting	2.022	0.677
Not-Worrying	2.356	1.064
Attention Regulation	2.900	0.715
Emotional Awareness	*3.420*	*0.727*
Self-Regulation	2.625	0.937
Body Listening	*2.178*	*0.973*
Trusting	3.733	0.854

3.3. Association between HEP amplitudes and MAIA scores

As there were no differences in mean HEP amplitudes and most of the MAIA scales between males and females, the search for association between measures was performed on the whole sample without splitting for sexes.

For each of eight MAIA scales, separate cluster-based permutation test on t-values of Pearson correlations between HEP amplitudes and scores was performed. From all MAIA scales, the strongest association was observed between HEP amplitudes and scores on the *Not-Worrying* scale: cluster-based permutation test indicated presence of correlations in the cluster at Cz in the time window from 400 ms to 545 ms after the R peak (permutations' conventional $p = 0.016$). The Pearson correlation between the individual *Not-Worrying* scores and the individual mean HEP amplitudes at 400-545 ms window was moderate ($r = 0.583$, $p = 0.0007$; see Figure 2), and it remained significant after controlling for potential influence from the autonomic nervous system (ANS) as measured by the heart rate variability (see Supplementary data 2). Similar pattern of correlations was observed for C4, Pz, P4 sites (see Supplementary data 3).

Cluster-based permutation tests did not result in any significant correlation clusters between HEP amplitudes and remaining seven MAIA scales (for *Noticing* all p-values above 0.67, for *Not Distracting* all $p > 0.73$, for *Attention Regulation* all $p > 0.28$, for *Emotional Awareness* all $p > 0.10$, for *Self-Regulation* all $p > 0.51$, for *Body Listening* all $p > 0.54$, for *Trusting* all $p > 0.52$).

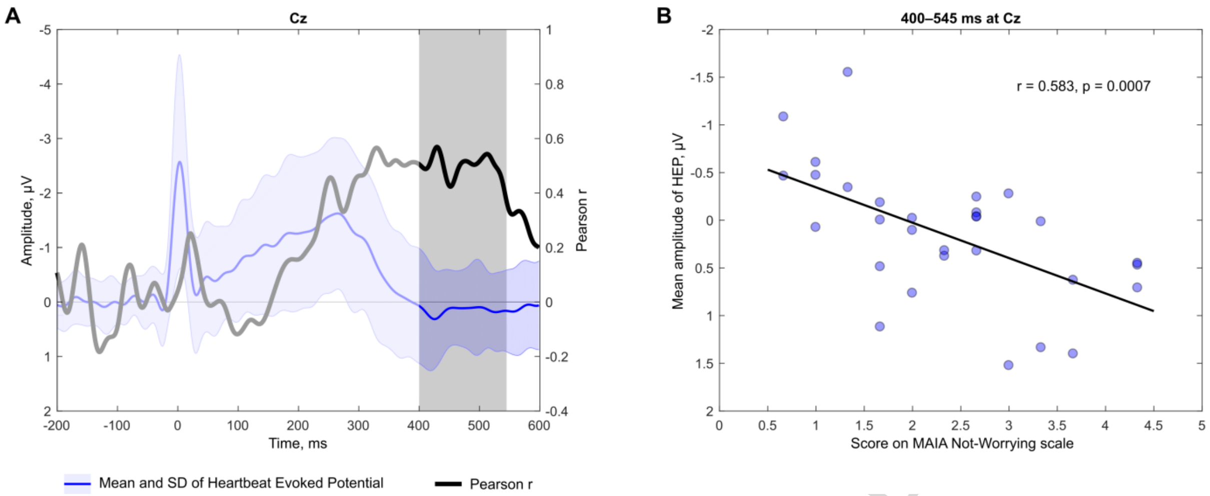

Figure 2. (**A**) The time course of the Pearson correlation coefficient *r* (bold line) between the individual HEP amplitudes (thin line – mean; shaded area – SD) and the ratings on the MAIA *Not-Worrying* scale. The grey area highlights the 400-545 ms time window in which a significant correlation between HEP amplitudes and *Not-Worrying* scores was indicated by cluster-based permutation test. **(B)** The association between individual mean HEP amplitudes during 400-545 ms interval from Cz electrode and individual scores on MAIA *Not-Worrying* scale.

4. Discussion

Our study aimed to evaluate the relationship between the late part of the heartbeat evoked potential (HEP) amplitudes and scores of the scales of *Multidimensional Assessment of Interoceptive Awareness (MAIA)* questionnaire to elucidate whether self-reported interoceptive abilities and tendencies (subjective indices of interoception) are related to the CNS representation of interoceptive processing (physiological indices of interoception). We show that the late HEP amplitudes are positively associated with the individual scores on the *Not-Worrying* scale of MAIA at Cz in the time window from 400 ms to 545 ms after the R peak. Moreover, this association is not related to the ANS influence, and the measures do not differ between sexes.

HEP amplitudes in the 400–600 ms time window after the EKG R peak were more positive at the central and parietal areas as compared to the frontal area. This observation is in accordance with Dirlich et al. [32], where peak HEP amplitudes were found at ~480 ms after the R wave mostly at parietal sites. Similarly to Dirlich et al. we did not observe significant laterality effect on the late HEP amplitudes. Our results are also in line with the observation by Schulz et al. [30] on higher mean HEP amplitudes in 455–595 ms window at Cz compared to Fz. Müller et al. [29] analyzed HEPs in 455–595 ms window and their healthy participants had somewhat higher (however non-significant) amplitudes at the vertex (Figure 1B in their paper). On the contrary, Pollatos et al. [31] reported higher amplitudes in 400–600 ms window over the frontocentral sites.

We hypothesized that individual differences in the qualitative aspects of interoception could be reflected in the late HEP amplitudes. Thus, for evaluation of associations between self-reported aspects and late HEP amplitudes, we applied cluster-based permutation statistics to identify significant location and time intervals. The only association that emerged was the positive correlation between the late HEP amplitudes at Cz and the *Not-Worrying* scale of MAIA: more positive late HEP amplitudes were associated to higher scores on the *Not-Worrying* scale.

The *Not-Worrying* scale of MAIA is defined as a "tendency not to worry or experience emotional distress with sensations of pain or discomfort" [7] and includes the following statements: "When I feel physical pain, I become upset", "I start to worry that something is wrong if I feel any discomfort", "I can notice an unpleasant body sensation without worrying about it". It is worth to mention, that the trait measured by the *Not-Worrying* scale reflect the basic ideas of *mindfulness* training, i. e. cultivating awareness and non-judgmental acceptance of body sensations [54–57].

The positive relationship between HEP amplitudes and *Not-Worrying* scale scores indicates that the intense CNS representation (higher HEP amplitudes) is associated with lower worries about bodily sensations. Worry, in turn, is tightly connected to the anxiety (e. g. somatic anxiety, rumination, neuroticism, trait anxiety) [58,59] – a cognitive state related to the inability to control emotional responses to perceived threats [60] that, according to Paulus and Stein, is a consequence of noisily amplified self-referential interoceptive predictive belief states [61] that are potentially reflected in CNS responses to internal signals (i. e. HEPs). This fits with the integrative multi-hierarchical model for the conscious and unconscious perception of emotional states proposed by Smith and Lane [62]: emotional feelings and non-emotional interoceptive / somatic perception share the same nervous inputs and are used to detect/represent coherent 'whole-body patterns' to form the representation of the emotional state. The inadequate CNS representation (or disturbed 'whole-body patterns') could lead to the greater 'noise' in the representation of emotional state and induce consciously perceived worries about bodily sensations [31].

Accordingly, the rumination (repetitive thoughts that may characterize anxiety) leads not only to difficulty in concentrating and decreased positive affect but also to the emotional sensitivity to stressors [63]. In line with that, the late HEP amplitudes (455 ms to 595 ms after EKG R) were previously shown to be modulated by stress and emotion regulation. Gray et al. [36] found that increased HEP negativity at the left temporal and lateral frontal electrodes was associated with stress-induced increments of cardiac output, although HEP amplitudes did not differ between resting and mental stress conditions. Müller et al. [29] showed that more positive HEP amplitudes at the parietal and occipital areas were associated with better emotion regulation (lower scores on *Emotional dysregulation* subscale of *Difficulties in Emotion Regulation Scale, DERS*), and with larger gray matter volume in the anterior insula and the dorsal anterior cingulate cortex (ACC).

Although current experimental setting do not allow to perform source localization to identify CNS structures involved in late HEPs, it is known that insula and ACC are among the cortical generators of HEPs [24,29]. The contribution from these structures to the current results is indirectly supported by the facts that insula and ACC are parts of the emotion regulation [64–70] and the anxiety related brain networks [58–60,71–74]. Moreover, the volume of these structures increases during both *Mindfulness Based Stress Reduction* therapies and long-term *mindfulness* meditation [75], i. e. with increase of the *Not-Worrying*.

Several limitations of the current study should be mentioned. First, the study sample was uniform and relatively young and it is not known if the observed relationship is present in other age groups. Also, subjects were highly motivated to participate in the experiment and were interested to gain additional knowledge and experience without reimbursement, suggesting a personal interest in body sensation perspective that could have effect on the subjective evaluation. The small number of males and females in the sample did not allow evaluation of associations for each sex separately and this should be performed in future studies. Additionally, future research should elaborate high-density EEG recordings to perform source-localization of structures contributing to the late HEP part.

Nevertheless, our results add to the number of prior attempts to establish the relationship between different indices of interoception. The majority of studies (e. g.: [20,22,23,26,27,76–78]) confirmed relationships between physiological / neuroimaging and behavioral indices. Meanwhile, studies assessing a combination of behavioral and self-report indices (e. g.: [9–11,41,42,79–85]) suggest independence of aspects of interoception. Similarly, we show that seven out of eight MAIA scales are not correlated to the late HEP amplitudes, this being in line with results of Mallorquí-Bagué et al. [42], who evaluated associations between self-reported and physiological indices of interoception. On the other hand, positive correlation between the *Not-Worrying* scores and late HEP amplitudes suggests that some of the qualitative aspects of interoception may be related to objectively assessed CNS representations. Altogether these give support to the multifaceted nature of interoception.

5. Conclusions

The late heartbeat evoked potential amplitudes are positively associated with individual scores on the *Not-Worrying* scale of MAIA at Cz in the time window from 400 ms to 545 ms after the R peak. This association is not related to the ANS influence, and the measures do not differ between sexes. No other self-reported indices of interoception are related to late HEP amplitudes, suggesting that scales and HEPs measure different aspects that are not directly interrelated. This supports the need to treat interoception as a multidimensional construct.

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The Authors declare that there is no conflict of interest.

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Highlights

- Relationship between late HEP amplitudes and scores of MAIA scales was investigated
- Late HEP amplitudes were positively associated with Not-Worrying scale scores
- No associations between late HEP amplitudes and other MAIA scales were found