Brain-heart dynamics in emotional regulation under uncertainty indexes depressive risk

- Short title

  Brain-heart reactivity indexes depressive risk

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Abstract

Recent studies highlight interoception as essential to processing healthy emotion and to pathology of major depressive disorder (MDD). It has been reported that interoceptive responses are impaired in MDD and in healthy individuals with a high depressive risk (HDR). However, it is unclear how individual differences in HDR relate to neurophysiological underpinnings for interoceptive and emotional reactions under different degrees of certainty. We examined whether HDR mediates the relationship between a neurophysiological marker for interoception, heartbeat-evoked potential (HEP), and an index for cardiac reactivity, heart rate (HR) or heart rate variability (HRV). In a concurrent EEG-ECG experiment, 26 healthy participants underwent an emotion-evoking picture-evaluation task. Each of differential auditory cues was associated with certainty of the upcoming pleasant or unpleasant picture. The results showed attenuated HRV activity for certain cues in HDR individuals. Neural and physiological reactions to uncertain, unpleasant pictures were enhanced by depressive risk. These results suggest reduced responses in prediction processing and enlarged precision-weighted prediction error for unpleasant pictures. Finally, HDR significantly mediated the HEP and HR relationship for unexpected unpleasant stimuli. This study provides evidence that interoceptive predictive coding in the cardiac domain is altered by HDR and suggests that investigating brain-heart interactions related to predictive coding will offer insights into how to estimate depressive risk.

1. Introduction

Emotions are affected by an external or internal events and are governed by the intrinsic force to maintain the current emotional state (Kuppens and Verduyn, 2017). Among various types of emotion, depression, or an emotional state marked by a constantly low mood, is characterized by an alternation of emotional processing. Accumulating evidence suggests that interoception, the perception of bodily states, is a key to understanding emotional processing and the pathology of major depressive disorder (MDD) (Critchley and Garfinkel, 2017). Behavioral (Eggart et al., 2019) and neuroimaging (Avery et al., 2014; Wiebking et al., 2015) studies of MDD patients have reported impaired interoceptive functions in MDD. While neural mechanisms in depression, particularly on emotional processing, have been extensively explored to date (Stuhrmann et al., 2011), investigations on the relationship between interoception and autonomic regulation have just begun.

Our cardiac autonomic systems automatically respond to emotional events. For example, heart rate (HR) (Ilves and Surakka, 2012; Brouwer et al., 2013) and heart rate variability (HRV) (Vaschillo et al., 2008; Kop et al., 2011) are well-known markers for cardiac reactivity that reflect changes in valence (pleasant or unpleasant emotional states). Heartbeat-evoked potentials (HEPs) on the other hand represent *neural* responses for each heartbeat and thought to reflect interoceptive cardiac processing in the brain (Park and Blanke, 2019; Coll et al., 2021). It has been suggested that generation of HEPs may reflect a projection of cardiac *afferent* signals from the heart to brain regions, such as the insula, where interoception is signaled from the vagus nerve and brainstem (Kern et al., 2013; Park et al., 2017; Salamone et al., 2020). Studies of brain-heart interactions have also reported that HEPs (Ravijts, 2019) and the coupling of brain theta activity and cardiac activity (Valenza et al., 2016) were modulated by emotion. Therefore HEP and HR/HRV are putatively great candidates for quantitative neuro-cardiac substrates for psychological/psychiatric risks.

The disturbance of interoceptive responses in MDD may be associated with an inefficient internal model, unreliable prediction errors, and inaccurate prediction of precision (Barrett et al., 2016). According to predictive coding theory (Friston and Kiebel, 2009; Friston, 2010; Seth et al., 2012), the brain constantly predicts future sensory inputs and updates the internal model to improve prediction (perceptual inference)

or acts based on the prediction errors (active inference). When updating the internal model, precision (of signals) is predicted to weight predictions and prediction errors, which can be implemented via attentional gain and neuromodulation (Feldman and Friston, 2010; Barrett, 2017). However, little is known about how individual differences in depressive risk mediate relationships among these three components (prediction, prediction error, and precision) during emotional anticipation and response.

In relation to the predictive coding theory, an increasing body of research suggests a link of MDD to interoceptive awareness. Individuals with 'high depressive risk (HDR)' who have elevated risks of developing MDD (Fergusson et al., 2005) show altered interoception, such as reduced HR recovery rate in response to unpleasant images (De Zorzi et al., 2021) and reduced connectivity in the brain interoceptive network (Hwang et al., 2015; Peng et al., 2020). In addition, abnormal anticipation of future events has been observed in individuals with HDR (Argyris Stringaris et al., 2015; He et al., 2019). Thus, alteration of interoceptive responses may span the entire spectrum, along with the depressive trait. As a part of the homeostatic function, the body auto-regulates even before the anticipatory event so as to minimize the prediction error (Sterling, 2012). At the neural level, preparatory activity is known, such that neurons fire even before the incoming sensory inputs (Kok et al., 2016; Livneh et al., 2020). It has also been proposed that cardiac regulation plays a role of a mediator to maintain homeostatic state of mind by reducing surprise against uncertainty (Corcoran et al., 2021). Previous studies have shown that *uncertainty* induced greater physiological (Murakami et al., 2010; Tracy et al., 2017) and neuro-cardiac responses (Marshall et al., 2017; Gentsch et al., 2019), especially when expecting negative items. However, it is yet unclear whether responses of the interoceptive neuro-*cardiac* system for certainty and uncertainty reflect individual differences in HDRs.

The present study investigated cardiac autonomic regulation of healthy individuals under certainty and uncertainty. Both electroencephalograms (EEG) and electrocardiograms (ECG) were monitored while participants performed an emotion-evoking picture-evaluation task. The pre-cue tone was played to induce anticipatory responses, followed by a display of either a pleasant or an unpleasant image. As an index of neuro-physiological interaction, HEP was assessed, and HR and HRV were assessed as indices of cardiac reactivity. Based on previous literature on cardiac reactivity, we used predictive coding theory to hypothesize that stimuli with *negative* valence (unpleasant pictures) under *uncertainty* would elicit larger

cardiac responses. Moreover, we speculated that HDR would mediate the relationship between the central processing of cardiac signals and cardiac reactivity indices. Altogether, we examined how cardiac and neurophysiological signals interact with interoceptive prediction and prediction errors in association with HDR.

2. Materials and Methods

2.1. Participants

Twenty-six healthy participants (16 females; mean and standard deviation (*SD*) of age: 22.19 ± 1.86 years old) with no history of psychiatric, psychological, or cardiac disorders, participated in concurrent EEG-ECG recording during an emotion-evoking picture-evaluation task. Data were acquired from a previous study (Machizawa et al., 2020).

2.2. Questionnaire procedure

The level of HDR was evaluated using the Japanese version of Beck Depression Inventory-II (Beck et al., 1996; Spielberger et al., 2003). The overall mean and *SD* of the BDI score were 5.65 ± 7.22. For display purposes for some data analyses, participants were split into two groups. Participants having BDI scores higher than the third quartile (BDI ≥ 5) and lower than the first quartile (BDI ≤ 2) were categorized into high depressive risk (HDR) and non-high depressive risk (non-HDR) groups, respectively. According to this criterion, 13 participants were categorized as non-HDR (BDI = 1.23 ± 0.89) and 8 as HDR (BDI = 14.12 ± 7.42).

2.3. Behavioral task and procedure

The emotion-evoking picture-evaluation experiment consisted of 240 trials. Each trial was comprised of a pre-cue and a picture-presentation phases followed by a subjective evaluation of valence. During the pre-cue (‘cue’ phase), an auditory tone was presented for 0.25 s, followed by a 3.75-s blank period. During a picture-presentation (‘pic’ phase), either a pleasant or an unpleasant picture was displayed for 4 s, in which participants were asked to evaluate the emotion they felt. Participants rated their emotional valence on a

four-point Likert scale (from most unpleasant to most pleasant) immediately after seeing a picture during the evaluation phase. Three different tones (low, mid, and high at 500, 1000, and 1500 Hz, respectively) were used as auditory pre-cues to indicate three predictive conditions: predictable pleasant (PP), predictable unpleasant (PU), and unpredictable (UX). The unpredictable condition contained two conditions based on the valence of the picture actually shown: unpredictable pleasant (UP) and unpredictable unpleasant (UU). Note that we abbreviate the conditions in this manuscript as follows: the letter X indicates the combination of possible conditions. For example, XP represents a combination of PP and UP conditions (pleasant picture conditions regardless of predictive tones), whereas PX represents a mixture of PU and PP conditions (predictable conditions regardless of the subsequent valence of the picture). The mid (1000-Hz) tone was the cue for the UX condition. The 500- and 1500-Hz tones were used in either PP or PU conditions (the assignment was counterbalanced across participants). Each of the three predictive conditions consisted of 80 trials. In the UX condition, 40 trials showed pleasant pictures (UP) and another 40 showed unpleasant pictures (UU). Pictures were selected from the International Emotional Picture System (IAPS) (Lang et al., 1997). Finally, participants rated their emotions after seeing the images. For further details, please refer to Machizawa et al. (2020).

2.4. EEG-ECG simultaneous recordings

During the task, brain and cardiac activity were simultaneously recorded using the BioSemi ActiveTwo system (BioSemi, Amsterdam) at a sampling rate of 2,048 Hz. The 64-channel EEG electrodes were placed according to the conventional international 10-20 montage. In addition to EEG channels, ECG electrodes were placed on the left wrist and right side of the back of the neck to monitor bipolar ECG signals. Additionally, a conventional bipolar electrooculograph (EOG) was monitored to measure vertical and horizontal eye movements. Four EOG electrodes were individually placed above and below the right eye and left and right of the outer canthi. An additional channel was placed at the tip of the nose for offline re-reference.

2.5. HR and HRV computation

Preprocessing and R peak detection from ECG signals were conducted using the Python package, BioSPPy (Carreiras et al., 2015). Raw ECG signals were first bandpass-filtered with an FIR filter with a passband

frequency range of 3–45 Hz, followed by detection (Hamilton, 2002) and location correction of R peaks by relocating each R peak to the time point with the maximum ECG signal within the time range of –50 to 50 ms.

Instantaneous heart rate (HR) was computed from the inverse of the inter-beat interval (IBI) between two successive R peaks. For subsequent analyses, instantaneous HR data points exceeding the physiological range (40–200 bpm) were discarded. Finally, time series of HR were obtained by applying boxcar smoothing with a window size of 3 and cubic spline interpolation to those instantaneous HRs.

As an HRV index, we employed *SD* of normal-to-normal IBI (SDNN) in the current study (Jennings et al., 1981; Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996; Berntson et al., 1997). To obtain the time series of HRV, IBIs with z-scores larger than 1.96 were discarded and then the remaining IBIs were up-sampled to 4 Hz using cubic spline interpolation. Then a 10-s sliding window with a 0.25-s step was applied to the interpolated IBIs to compute the *SD* of IBIs within the window as the instantaneous HRV value at the center of the window. The resulting 4-Hz time series of HRV was further up-sampled to the original sampling rate of EEG at 2,048 Hz to match the sampling rate. We set the following rejection criteria to assure the quality of HR and HRV indices. Epochs of HR and HRV were extracted between 1 s before and 20 s after cue display onset. For each participant, two types of outliers were detected across and within trials and discarded according to robust z-score criteria: (1) *epochs* with absolute robust z-scores larger than a threshold of 3.4807 (equivalent to $p = .0005$) after applying a robust z transform to mean values of all epochs, and (2) epochs with robust z-scores of any *sample* larger than the threshold after applying a robust z transform to the time series within the same epoch. These cleaned data were employed in subsequent analyses. The remaining epochs of HR and HRV were downsampled to 200 Hz and averaged across epochs of the same condition within participants for subsequent analysis.

2.6. HEP computation

EEG signals were preprocessed using EEGLAB toolbox v2019.1 for Matlab (Delorme and Makeig, 2004). Continuous raw data were bandpass-filtered (1–40 Hz), downsampled to 256 Hz, epoched to cue-onset (–1 s to 10 s), and baseline-corrected (–1 s to 0 s). Artifactual epochs were detected by the automatic rejection

algorithm implemented in EEGLAB. Eye-related artifacts were corrected using automatic EOG correction with conventional recursive least squares regression. An extended Infomax-independent component analysis was performed to remove EOG- and ECG-related components. Noise-free epochs were then re-referenced to the average reference of EEG signals.

For each of the EEG epochs, the time of R peaks was detected from corresponding bandpass-filtered ECG signals for two periods 0.5–3.4 s after cue-onset (within the cue phase) and 4.5–7.4 s after cue-onset (equivalent to 0.5–3.4 s after picture-onset; during the pic phase). In this study, the R peaks close to cue and picture presentations were not applied to HEP computation in order to minimize direct perceptual effects of auditory and visual stimuli, respectively.

EEG-ECG epochs containing falsely detected R peaks were detected and discarded based on careful visual inspection. For retained EEG-ECG epochs, time points of R peaks were used as the onset time to further epoch EEG signals (–0.1 to 0.6 s), followed by baseline correction (–0.1 to 0 s). HEPs were then computed for corresponding conditions during the cue and pic phases separately. Note that onset times of HEP signals were the time points of R peaks, as per convention, while that of cardiac reactivity was the time of cue display onset.

To identify morphology of HEPs, surrogate HEPs were computed based on surrogate R-peaks that were randomly jittered in a range of –0.1 to 0.1 s from the time points of real R peaks (Gentsch et al., 2019). HEPs and surrogate HEPs of each participant were then individually averaged across all epochs regardless of condition. A nonparametric cluster-level F-test for spatiotemporal data implemented in MNE-Python (Gramfort et al., 2013) was then applied to the averaged HEP and averaged surrogate HEP waveforms to identify clusters of channels and time periods revealing significant neural responses to heartbeats within the time-window of 0.1 to 0.6 s after the R-peak onset. Any electrodes located within 5 cm of each other were considered spatial neighbors. The number of permutations was set to 2,500 and the threshold to form clusters was an F-value corresponding to an uncorrected *p*-value of .00001.

2.7. Statistical analysis

2.7.1. Effects of cues or emotional pictures on HR and HRV

To identify the period showing significant main effects of cues and emotional pictures, repeated-measures ANOVA (RM-ANOVA) with post hoc tests on the HR or HRV was performed for each time point, followed by multiple comparison correction using the false discovery rate (FDR). Since recovery duration (waveform returned to baseline) for HR and HRV appeared to differ, we considered different time-windows for HR and HRV: 12 s for HR waveform and 20 s for HRV waveform. The above-mentioned statistical procedure was conducted on HR and HRV time series for both non-HDR and HDR groups for all participants. In this study, computation of RM-ANOVA, *t*-tests and FDR correction were performed using implementations in the Python packages, pingouin (Vallat, 2018), SciPy (Virtanen et al., 2020), and statsmodels (Seabold and Perktold, 2010), respectively. In this study, our α-level for FDR-corrected *p*-values ($p_{\text{FDR-corrected}}$) was set at 0.05. As necessary, uncorrected *p*-values ($p_{\text{uncorrected}}$) less than 0.05 were also reported to show the trend for completeness.

2.7.2. Effects of certainty and valence at anticipation and perception stages

Effects of certainty on cardiac reactivity were further examined on anticipation and perception stages. Time periods of the two stages were determined based on durations showing a significant main effect of cue and valence of pictures. If no significant main effect was found during the cue phase, the whole time period 0–4 s during the cue phase was averaged. RM-ANOVA on averaged HR or HRV for various cues was performed at both stages. For each stage, the effect of certainty on cardiac reactivity was assessed between certain (PP and PU) and uncertain (UP and UU) conditions using paired *t*-tests. Moreover, the *certainty effect* was also assessed on the *difference* of time-averaged cardiac reactivity between the predictable and unpredictable conditions followed by the display of unpleasant pictures (PU – UU) and pleasant pictures (PP – UP), regardless of valence (PX – UX).

Effects of valence on HR and HRV were also examined for each stage. The procedure was similar to that for analyzing the effect of certainty. Durations showing a significant main effect of the picture were used to determine the durations of the anticipation and perception stages. RM-ANOVA on the averaged HR or HRV for various valences at the two stages was performed. For each stage, the comparison of cardiac

reactivity between pleasant (PP and PU) and unpleasant (PU and UU) conditions was assessed using paired *t*-tests. The *valence effect* was also computed as the *difference* of time-averaged cardiac reactivity between pleasant and unpleasant picture conditions, in regard to high certainty (PP – PU), low certainty (UP – UU), and a mixture of the two (XP – XU). Effect sizes of RM-ANOVA and paired *t*-tests were measured using partial eta-squared (η^2) and Hedges' *g*, respectively.

2.7.3. Interrelationships between HDR, cardiac reactivity, and HEP

To qualify the relationship between HDRs and cardiac reactivity, the partial correlation between BDI scores and cardiac reactivity was computed for every stage and condition, using the Python package pingouin (Vallat, 2018), and was controlled for age and sex. Also, partial correlations between BDI and the valence effect and between BDI and the certainty effect were computed. Moreover, for each index of cardiac reactivity, a comparison between non-HDR and HDR groups was performed using two-sample *t*-tests. In this study, effect sizes of two-sample *t*-tests and partial correlation were measured using Hedges' *g* and r^2, respectively.

The raw amplitude of HEP under each condition at each phase was compared between non-HDR and HDR groups with two-sample *t*-tests, and its relationships to HDR and cardiac reactivity at the perception stage were examined using partial correlation, controlled for age and sex. As we were to compare individual differences in HEP amplitude, to reduce the bias of individual's EEG signal amplitude due to skull thickness or scalp conductivity (Picton et al., 2000), the difference of HEP amplitude between picture ('pic') and cue phases (pic – cue difference), between unpleasant and pleasant conditions (valence effect), and between predictable and unpredictable conditions (certainty effect) for each spatiotemporal cluster was also computed to examine the effect of HDR on HEP. The group difference of HEP between non-HDR and HDR groups was compared using two-sample *t*-tests. The relationship between HDR and HEP was computed with partial correlation to BDI, controlled for age and sex. Furthermore, the partial correlation between the pic – cue difference of HEP and cardiac reactivity at the perception stage was computed. The partial correlation between the valence effect of HEP at the cue or pic phase and the valence effect of cardiac reactivity at the perception stage was computed under predictable and unpredictable conditions. The partial correlation between the certainty effect of HEP at the cue or pic phase and the certainty effect

of cardiac reactivity at the perception stage was computed under pleasant picture and unpleasant picture conditions.

For conditions showing a significant correlation between HR/HRV/HEP and HDR or showing a significant difference between non-HDR and HDR groups, mediation analysis implemented in pingouin (Vallat, 2018) was applied to examine the following model: the relationship between the HEP and cardiac reactivity mediated by HDR, controlled for age and sex.

3. Results

3.1. Effects of valence, uncertainty, and HDR on HR

HR slightly increased after cue display onset and then decreased (Figure 1a). HR time series were strongly modulated by emotional pictures from 5.4–10.7 s after cue presentation ($p_{\text{FDR-corrected}} < .05$ and duration > 1 s in cue × pic RM-ANOVA for the main effect of pic). During this period, unpleasant pictures elicited a larger deceleration of HR than pleasant pictures, especially in the unpredictable condition ($p_{\text{FDR-corrected}} < .05$ and duration > 1 s in post hoc analysis for the main effect of pic). Modulation of HR time series by emotional pictures also occurred in the HDR group at 4.2–7.1 s and 8.5–11.9 s (Figure 1c), but not in the non-HDR group (Figure 1b). HR time series were also modulated by cue at the cue phase (1.7–3.0 s) and the pic phase (8.2–9.7 s) ($p_{\text{uncorrected}} < 0.05$ and duration > 1 s in cue × pic RM-ANOVA for the main effect of cue). Greater acceleration of HR at 1.7–3.0 s (UX > PP) and smaller deceleration at 8.2–9.7 s (UP < PP and UX < PU) appeared in unpredictable conditions than in predictable conditions. Modulation of HR time series by cue was also observed at 0.8–4.7 s and 7.7–12.0 s in the non-HDR group, but not in the HDR group ($p_{\text{uncorrected}} < .05$ and duration > 1 s). Moreover, both the cue and pic modulated HR time series at 2.3–3.5 s ($p_{\text{uncorrected}} < 0.05$ and duration > 1 s in cue × pic RM-ANOVA for the interaction of cue and pic).

HR differed significantly between anticipation stage (1.7–3.0 s) and perception stage (8.2–9.7 s) in unpleasant picture conditions (PU and UU, F = 26.04, $p < .001$, $\eta^2 = .51$, in stage × cue RM-ANOVA for main effect of stage) and also pleasant picture conditions (PP and UP, F = 20.19, $p < .001$, $\eta^2 = .45$) (Figure 2a). Significantly reduction of HR from anticipation stage to perception stage was found in the unpleasant conditions ($t = 7.09$, $p < .001$, Hedges' $g = 1.64$, in post hoc analysis for the main effect of

stage) and pleasant conditions (t = 6.18, p < .001, Hedges' g = 1.36). HR was significantly different between certain and uncertain cue conditions for pleasant picture conditions (F = 7.14, p = .013, η^2 = .22 in stage × cue RM-ANOVA for main effect of cue), but not for unpleasant picture conditions (F = 0.06, p = .813, η^2 < .01). In pleasant picture conditions, unpredictive cues induced higher HR than predictive cues (PP < UP, t = 6.18, p < .001, Hedges' g = 1.36 in post hoc analysis for the main effect of cue) and the difference of HR responses to the two types of cues was prominent at the anticipation stage (t = 2.63, $p_{\text{uncorrected}}$ = .014, $p_{\text{FDR-corrected}}$ = .021, Hedges' g = .26, in paired t-test).

A significant difference in HR responses between the anticipation stage (0–4.0 s) and the perception stage (5.4–10.7 s) was also found in predictive cue conditions (PU and PP, F = 29.86, p < .001, η^2 = .54, in stage × valence RM-ANOVA for main effect of stage) and unpredictive cue conditions (UU and UP, F = 33.22, p < .001, η^2 = .57) (Figure 2b). HR decreased from the anticipation stage to the perception stage in the predictive cue conditions (t = 7.44, p < .001, Hedges' g = 1.57, in post hoc analysis for the main effect of stage) and unpredictive cue conditions (t = 7.79, p < .001, Hedges' g = 1.63). HR responses were also strongly modulated by valence (F = 11.64, p = .002, η^2 = .32, in stage × valence RM-ANOVA for main effect of valence). Higher HR was observed in the pleasant picture condition than the unpleasant picture condition (UP > UU, t = 7.79, p < .001, Hedges' g = 1.63, in post hoc analysis for main effect of valence) and the difference of HR responses to the two types of pictures was prominent at the perception stage (t = 3.45, $p_{\text{uncorrected}}$ = .002, $p_{\text{FDR-corrected}}$ = .006, Hedges' g = .72, in paired t-test).

At the anticipation stage, HR responses were not altered with the HDR (in two-sample t-test for non-HDR and HDR groups and in partial correlation analysis between BDI and anticipatory HR). At the perception stage (5.4–10.7 s), HR changes in the UU and XU conditions were significantly correlated with BDI scores (Figure 2c and Table 1). Moreover, the induction valence effect under unpredictable conditions (UP – UU) was also significantly correlated with BDI scores (r = .43, p = .036, r^2 = .185). Furthermore, unpleasant pictures significantly induced larger deceleration of HR in the HDR group than in the non-HDR group (t = 5.41, $p_{\text{uncorrected}}$ < .001, Hedges' g = 2.08 for UU and t = 3.86, $p_{\text{uncorrected}}$ < .001, Hedges' g = 1.52 for XU in two-sample t-tests).

3.2. Effect of valence, uncertainty, and HDR on HRV

HRV increased after cue display onset, exceeded the maximum peak at around 10 s, and then recovered at around 20 s (Figure 3a). HRV time series were strongly modulated by emotional pictures at 14.8–16.1 s ($p_{\text{FDR-corrected}} < .05$ and duration > 1 s in cue × pic RM-ANOVA for the main effect of pic). Modulation of HRV time series was also observed in the non-HDR group at 10.0–15.8 s ($p_{\text{FDR-corrected}} < .05$ and duration > 1 s in cue × pic RM-ANOVA for the main effect of pic), but not in the HDR group. In the non-HDR group, modulation of HRV time series by emotional pictures was prominent in unpredictive conditions, UP > UU, at 9.9–16.0 s ($p_{\text{FDR-corrected}} < .05$ and duration > 1 s in post hoc analysis for the main effect of pic).

HRV time series were not significantly modulated by the cue ($p_{\text{uncorrected}} < .05$ and duration > 1 s in cue × pic RM-ANOVA for the main effect of cue). The interaction of cue and emotional picture also was not observed. In the non-HDR group, HRV time series were modulated by cue at 2.9–5.7 s (Figure 3b), while modulation of HRV time series by cue was observed in the HDR group at 1.5–3.2 s and 9.2–12.1 s ($p_{\text{uncorrected}} < .05$, duration > 1 s in cue × pic RM-ANOVA for the main effect of cue) (Figure 3c). HRV differed significantly between predictable and unpredictable conditions at the cue phase, but the trend in the non-HDR group (PU > UX at 2.9–5.7 s, $p_{\text{uncorrected}} < .05$, duration > 1 s in post hoc analysis) and that in the HDR group (PU < UU and PU < UX at 1.5–3.2 s) were reversed.

By combining time periods showing significant main effects of the cue in the non-HDR and HDR groups, 1.5–4.0 s and 9.2–12.1 s were selected as the anticipation and perception stages to further examine the effects of cue and stage. The HRV was strongly modulated by stage in both unpleasant picture conditions (PU and UU, F = 7.63, $p = .011$, $\eta^2 = .23$ in stage × cue RM-ANOVA for the main effect of stage) and pleasant picture conditions (PP and UP, F = 23.38, $p < .001$, $\eta^2 = .48$). In pleasant picture conditions, the HRV was strongly modulated by cue (F = 5.62, $p = .026$, $\eta^2 = .18$ in stage × cue RM-ANOVA for the main effect of cue) and an interaction of cue and stage (F = 9.02, $p = .006$, $\eta^2 = .27$ in stage × cue RM-ANOVA) was also observed.

Based on the results of main effect of picture from all participants, 0–4.0 s and 10.0–15.8 s were selected as the anticipation and perception stages for further examination of the effects of valence and stage. HRV was strongly modulated by stage in both predictive cue (PU and PP, F = 9.61, $p = .004$, $\eta^2 = .28$ in stage ×

cue RM-ANOVA for the main effect of stage) and unpredictive cue (UU and UP, F = 12.44, p = .002, η^2 = .33) conditions. The interaction of cue and stage was found in the unpredictive cue conditions (F = 7.79, p = .010, η^2 = .24 in stage × cue RM-ANOVA). At the perception stage, UP pictures elicited larger HRV increases than did PP pictures (9.2–12.1 s, t = 2.87, $p_{\text{uncorrected}}$ = .008, $p_{\text{FDR-corrected}}$ = .012, Hedges' g = .53 in paired t-test) and UU pictures (10.0–15.8 s, t = 2.46, $p_{\text{uncorrected}}$ = .021, $p_{\text{FDR-corrected}}$ = .032, Hedges' g = .53) (Figures 4a and 4b, respectively).

At the anticipation stage (1.5–4.0 s), reduced HRV responses to either pleasant or unpleasant stimuli under predictable conditions were correlated with HDR (Figure 4c). Under unpredictable conditions, anticipatory HRV responses were not correlated with BDI scores (Figure 4c). Moreover, compared to the non-HDR group, the HDR group showed significantly low anticipatory HRV responses in PU conditions (t = 4.37, $p_{\text{uncorrected}}$ = .001, Hedges' g = 1.53 in two-sample t-tests) and a reversed certainty effect under unpleasant picture conditions, PU – UU (t = 2.92, $p_{\text{uncorrected}}$ = .010, Hedges' g = 1.04) (Supplementary Table 1). Thus, anticipatory HRV responses in predictable conditions varied with the level of HDR.

At the perception stage of 9.2–12.1 s, the certainty effect on the processing of unpleasant pictures, PU – UU, was significantly stronger in the HDR group than in the non-HDR group (t = 2.36, $p_{\text{uncorrected}}$ = .003, Hedges' g = 1.35 in two-sample t-test) and significantly correlated with BDI scores (r = –.49, p = .016, r^2 = .238 in partial correlation analysis)(Table 2). At the perception stage of 10.0–15.8 s, the valence effect in unpredictable conditions (UP – UU) was larger in the non-HDR group than the HDR group (t = 3.37, $p_{\text{uncorrected}}$ = .003, Hedges' g = 1.36) and was negatively correlated with HDR (r = –.60, p = .002, r^2 = .359) (Supplementary Table 2). Moreover, HRV changes in the UU condition averaged over 9.2–12.1 s (Table 2) and over 10.0–15.8 s (Supplementary Table 2) were both significantly higher in the HDR group than in the non-HDR group and positively correlated with the level of HDR. The HRV in the UU condition in the HDR group was relatively higher than in the other three conditions (Figure 3c), but that in the non-HDR group was relatively lower than in the other three conditions (Figure 3b). Thus, perceptual HRV responses in the UU condition largely changed with the level of HDR.

3.3. Spatiotemporal clusters of HEP

Comparing the grand averages of the original HEP and surrogate HEP time series, the original one appeared to evoke stronger signals than the surrogate one (Figure 5a). In the nonparametric cluster-level test over original HEP and surrogate HEP spatiotemporal data ($p < .05$, duration > 0.1 s, number of channels >= 3), three significant spatiotemporal clusters were observed over (1) the occipital and left temporoparietal regions from 0.10–0.40 s, (2) the central region from 0.10–0.29 s, and (3) the right temporal regions from 0.23–0.37 s (Figure 5b). Cluster 1 showed a positive deflection, while clusters 2 and 3 showed negative deflections.

3.4. Effect of HDR on HEP cluster

The mean amplitude of the HEP cluster was non-significant between the non-HDR and HDR groups (Figure 6a). However, the partial correlation analysis demonstrated that weak amplitude of HEP clusters 1 and 3 correlated with the HDR when processing unpredictive cues (UX condition) (Supplementary Table 3). Furthermore, compared to the non-HDR group, the HDR group revealed a significantly larger pic – cue difference in HEP cluster 3 under the UU condition ($t = 3.19$, $p_{\text{FDR-corrected}} = .033$, Hedges' $g = 1.49$ in two-sample t-test) (Figure 6b). In the HDR group, the negative component of HEP in the UU condition increased at the pic phase compared to the cue phase (Figure 7d). In contrast, the HEP of the non-HDR group in the UU condition decreased at the pic phase. The results of partial correlation analysis further support that the pic – cue difference of cluster 3 enlarged as the HDR increased (Table 3).

In unpleasant picture conditions, the certainty effect found in cluster 3 at the pic phase was significantly larger in the HDR group than in the non-HDR group (PU – UU, $t = 3.71$, $p_{\text{FDR-corrected}} = .006$, Hedges' $g = 1.46$) (Figure 6c). Under unpleasant picture conditions, unpredictable pictures elicited greater HEP amplitude than predictable pictures in the HDR group, while HEP amplitude elicited by the two types of pictures was similar in the non-HDR group (Figures 7b and 7d). However, a significant partial correlation between the certainty effect and the HDR was found only in cluster 1 at cue phase under unpleasant picture conditions (PU – UU, $r = .45$, $p_{\text{uncorrected}} = .038$; see also Supplementary Table 4).

In predictable conditions, the valence effect found in cluster 3 at the cue phase was significantly larger in the HDR group than in the non-HDR group (PU – PP: t = 3.10; $p_{\text{FDR-corrected}}$ = .034; Hedges' g = 1.41; Figure 6d). Unpleasant stimuli also elicited greater HEP amplitude than pleasant stimuli in the HDR group, while unpleasant stimuli elicited lesser HEP amplitude than pleasant stimuli in the non-HDR group (Figure 8). No significant partial correlation was found between the valence effect and the HDR (Supplementary Table 5).

3.5. Correlation between HEP cluster and cardiac reactivity

In the UU condition, the mean amplitude of HEP clusters 1 and 2 at pic phase was correlated with HR changes at the pic phase (5.4–10.7 s) (Table 4) and that of HEP cluster 3 at cue phase was significantly correlated with HRV changes at the pic phase (9.2–12.2 s) (Supplementary Table 6). In the PP condition, pic – cue differences in HEP cluster 3 were negatively correlated with the change of HRV at the pic phase (Supplementary Table 7). This indicated that the larger negativity of HEP amplitude in cluster 3 at the pic phase was associated with larger HRV responses under the PP condition.

In the PP – UP conditions, certainty effects on the HEP cluster 1 at the pic phase and cue phase were negatively correlated with the certainty effect on HR and HRV changes, respectively (Supplementary Table 8). This indicates that in pleasant picture conditions, a larger certainty effect on the HEP amplitude of cluster 1 at the pic and cue phase caused a smaller certainty effect on the HR and HRV changes, respectively. In the PU – PP conditions, valence effects on the HEP cluster 3 at the pic phase and on the cluster 1 at the cue phase were negatively correlated with the valence effect on HR changes and HRV changes, respectively (Supplementary Table 9). In other words, in predictable conditions, larger valence effects on the HEP amplitude of cluster 1 at the cue phase and cluster 3 at the pic phase caused larger valence effects on the HRV and HR, respectively.

3.6. Mediation analysis

Table 1 and 2 show that HR and HRV responses in the UU condition at the perception stage reflected HDRs, respectively. The mean HEP amplitude at cue phase under the UX condition and the pic – cue difference in the UU condition in cluster 3 were altered with HDR (Supplementary Table 3 and Table 3).

In the UU condition, the mean HEP amplitude at cue phase showed a tendency to predict cardiac reactivity at the pic phase (Table 4 and Supplementary Table 6). Thus, we further examined the mediation effect of HDR on the relationship between HEP of cluster 3 and cardiac reactivity in the UU condition. This analysis showed that the indirect effect of mean HEP amplitude on HR changes mediated by HDR was significant, whereas the direct effect was non-significant (Figure 9a). Moreover, the indirect effect of pic – cue HEP amplitude difference on HR changes mediated by HDR was significant, whereas the direct effect was non-significant (Figure 9b). On the other hand, indirect and direct effects of HEP cluster 3 on HRV changes mediated by HDR were both non-significant when using pic – cue HEP amplitude difference or mean amplitude of HEP. This suggests that the HDR fully explained the association between HEP responses and HR changes, but not HRV changes, in the UU condition.

4. Discussion

This study examined the extent to which HDR is associated with cardiac and neurophysiological emotional responses in certain and uncertain circumstances. A comprehensive temporal characterization of HR, HRV, and HEP responses revealed dissociable and unique relations between certainty of predictive cues and emotional valence of pictures in the HDR and non-HDR groups. These results support the hypothesis that HDR alters processes for interoceptive predictive coding and increases the fluctuation of physiological responses against unpredictable stimuli. It appears that HDR influences anticipatory HRV and HEP responses and mediates the relationship between the HEP and HR especially responding to UU pictures (unexpectedly confronting a negative picture). These results indicate that HDR reduces neural resources for prediction processing and causes large prediction errors against unpredictable negative events. The present study offers evidence for the disturbance of interoception as an indicator of HDR.

Here, in congruent with the previous report that depression is associated with dysfunction in allostatic regulation (Barrett et al., 2016), the HRV responses for predictive cues were dissociable between the HDR and non-HDR groups (Figures 3b–c and 4c). As a cardiac reactivity index, SDNN is thought to reflect the activity of the parasympathetic (PNS) and sympathetic nervous systems (SNS) (Shaffer and Ginsberg, 2017). Moreover, low resting HRV has been associated with high emotional regulation difficulty and HDR

(Williams et al., 2015; Fantini-Hauwel et al., 2020). Thus, attenuated anticipatory HRV implies low cognitive flexibility (Gillie et al., 2015; Colzato et al., 2018) and autonomic capacity to regulate emotion in the HDR group. Allostasis involves prediction of body state responding to future events and preparation of the body before actual needs arise. According to the Embodied Predictive Interoception Coding model (Barrett and Simmons, 2015), allostatic and anticipatory responses are modulated by interoceptive predictions arising from the anterior insula (aINS), middle/anterior cingulate cortex (MCC/ACC), and ventromedial prefrontal cortex (vmPFC). Among them, aINS and ACC activity is altered in both subclinical depression and MDD (Hwang et al., 2015; Besteher et al., 2020). Connectivity of the vmPFC to the aINS and MCC also covaries with SDNN (Schumann et al., 2021). Thus, increased anticipatory HRV in the non-HDR group enables preparation of physiological status for upcoming stimuli. Attenuated anticipatory HRV may indicate inefficient allostatic regulation in the HDR group.

Moreover, the HDR group showed larger HEPs during anticipation of unpleasant pictures compared to pleasant pictures at the right frontotemporal electrode cluster, proximal to the INS (Figure 6d and 8). In the other words, an interoceptive response bias around this region was found only for *negative* valence, but not for positive valence. It has been reported that individuals with HDR may have altered anticipatory responses in the INS, ventrolateral PFC, ACC, and ventral striatum (Argyris Stringaris et al., 2015; He et al., 2019). The INS is considered as one of major neural sources underlying HEP (Park et al., 2017), and is responsible for processing prediction and prediction error of current and future physiological status (Tracy et al., 2017; Livneh et al., 2020). Thus, our findings provide additional neurophysiological evidence for alterations associated with HDR in interoception.

The HDR group showed the *enhanced* valence effect on anticipatory HEP (Figures 6d and 8) and *attenuated* HRV responses to *predictive* cues (Figure 4c). This may be caused by inefficiency of their prediction model (Barrett et al., 2016), including low precision of predictive signals and/or deviated prior belief (Edwards et al., 2012; Badcock et al., 2017). Precision, or the inverse of uncertainty, is built on the reliability of environment and modulated by attention (Park and Blanke, 2019; Petzschner et al., 2019; Coll et al., 2021). Precision is predicted in the high hierarchy and is top-down signaled to low-level areas that determine which prediction errors merit attention (Feldman and Friston, 2010; Barrett, 2017). When updating the prediction model, precision modulates the weights of predictions and evidence from sensory

inputs (Seth and Friston, 2016; Haarsma et al., 2021). The amplitude of HEP is considered a neural correlate of prediction processing (Ainley et al., 2016; Pfeiffer and De Lucia, 2017). For example, HEP amplitude appeared to be enhanced when participants attended to heartbeats, comparing to external stimuli (Petzschner et al., 2019). Enhanced attention to a specific signal can increase the precision and then increases the weight of the associated prediction error. Thus, enhanced HEP in HDR individuals during anticipation of *unpleasant* pictures may reflect their attentional bias to negative valence. Moreover, attenuated anticipatory HRV responses in HDR group may also imply their low precision and/or inaccurate prediction, which is inefficient at triggering appropriate autonomic regulations in response to possible upcoming events. Altogether, our results imply that HDR is associated with 'reduced precision' or 'deviated prior belief' for interoceptive prediction, which may emerge from discrepancies between prediction and prediction error for a long time in the lives of HDR individuals (Badcock et al., 2017).

We also observed a notable difference in the *changes* in HEP before (cue-phase) and after (pic-phase) the onset of target stimuli. The HDR group largely showed *increasing* frontotemporal HEPs from the cue-phase to pic-phase (Figure 6b and 7d), putatively reflecting enhanced brain-heart interactions of prediction error derived from the Insular network. The HDR group also showed large certainty effects on the same frontotemporal HEPs for *unpleasant* pictures (Figure 6c). Consistent with previous studies, *uncertain* stimuli enhanced HEP amplitude (Marshall et al., 2017; Gentsch et al., 2019). During the heartbeat counting task, HEPs reflected the precision-weighted prediction error for each heartbeat (Banellis and Cruse, 2020). Moreover, attentional bias for negative events might be notable characteristics of individuals with MDD (Gotlib and Joormann, 2010) and with subclinical depression (Lin et al., 2019). It has been shown that depressive trait may relate to *reduced* precision in prediction and *increased* precision in prediction error (Badcock et al., 2017). Thus, changes in HEP from cue to pic phases in HDR individuals may highlight 1) their *negative* bias in predictive coding processing and 2) their *increased* precision in prediction error or *reduced* precision of prediction signals.

As reported by a literature (De Zorzi et al., 2021), HDR was also associated with enhanced cardiac reactivity when processing negative events in the UU condition in our study (Figures 1c, 2c and 3c). HDR individuals also showed enhanced frontotemporal HEPs in response to UU pictures (Figure 6b). These effects observed in the UU condition may be interpreted in three ways. First, frontotemporal HEPs reflect

the precision weighting process and the HDR group overestimates weights for prediction errors elicited by UU pictures, inducing strong autonomic cardiac responses. The overestimated weight also highlights their negative attentional bias (Gotlib, 1983). Second, low interoceptive sensibility of visceral afferent signals during the cue phase enlarges the prediction error. MDD patients show reduced sensitivity in heartbeat perception due to low HEP amplitude (Terhaar et al., 2012) and low precision to cardiac afferent signals (Smith et al., 2020). The results of computational modeling also implied that inaccurate precision of incoming signals and prediction errors is the main source of interoceptive disturbance in MDD (Smith et al., 2021). Third, increased neural responses for UU pictures may be linked to enhanced autonomic control of cardiac dynamics, in subclinical depression during resting states (Catrambone et al., 2021). Moreover, the relationship between frontotemporal HEPs and HR was mediated by the BDI score (Figures 9a–b). Altogether, these sets of evidence suggest that HDR may be captured by monitoring the altered regulation of neurocardiac interoceptive processes against unexpected negative events. Such hypersensitivity of interoceptive prediction error may highlight their lowered resilience against stressors (Southwick et al., 2005); however, further investigations would be needed to reveal the relationship of the marker to the resilience.

We also examined temporal characteristics of HR changes for certainty of predictive cues and emotional valence of perception: the main effect of cues on HR appeared from 1.7 s and differential deceleration of HR between emotional pictures appeared at around 5.6 s, followed by the recovery of HR after 10 to 12 s (Figure 1). It is well known that activation of PNS decreases HR, whereas activation of SNS increases HR. The PNS exerts its effect on cardiac signals after 1 s, while the SNS exerts its effect after 5 s (Shaffer and Ginsberg, 2017). Thus, HR deceleration initiated during the cue phase may be modulated mainly by activated PNS and the recovery of HR may reflect the activation of the SNS. Our post hoc analysis further confirmed earlier findings that pictures of negative valence *decelerated* HR more than those of positive valence (Pollatos et al., 2007; Bradley et al., 2008; Ilves and Surakka, 2012; Brouwer et al., 2013). Some studies reported larger deceleration of HR for unpredictable stimuli than for predictable ones (Murakami et al., 2010; Tracy et al., 2017). Instead, we found the opposite trend, that HR deceleration in response to unpredictable pictures was smaller than to predictable pictures. This may result from different durations of baseline correction (Jennings et al., 1981). Various previous studies used the period before the presentation of pictures as baseline. Since anticipation induces changes of physiological activity (Pastor et al., 2014;

Pulopulos et al., 2018), our design may be more sensitive to effects of anticipation. Together with our findings of HRV, we provide evidence that modulation of cardiac activity initiates during the anticipation stage, suggesting that research on physiological activity should consider effects of anticipation, if various predictive cues are applied.

Despite our comprehensive analyses, this study has several limitations. First, since it was not feasible for our event-related paradigm and because it has been suggested that accurate measures of SDNN can be obtained from 10-s ECG recordings (Munoz et al., 2015; van den Berg et al., 2018), we computed temporal dynamics of HRV using a 10-s sliding window. Our analysis of HRV may not be directly comparable to the standard short-term HRV from 5-min ECG recordings (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). Second, our analysis of cardiac reactivity was limited to two time-domain parameters, HR and SDNN. As cardiac reactivity markers for HRV, frequency-domain parameters, such as low- or high-frequency components or non-linear geometric method (Shaffer and Ginsberg, 2017) might be possible. However, these measures typically require ECG recordings of at least 60 s are necessary (Munoz et al., 2015), so they would not fit well with our experimental design. Therefore, future studies could assess this using different experimental designs, such as a blocked design with longer inter-trial-interval rather than the event-related design we employed here. Third, although we tried to dissociate event-related effects of cue and picture on cardiac reactivity, temporal dissociation might not be perfectly achievable because of the fixed time interval between cues and pictures in our paradigm. Further investigations would be required to disentangle the temporal characterization of these effects. Although limitations and discrepancies exit in this study, our evidence supports the notion that HDR affects interoceptive cardiac processing responding to cues and emotional pictures.

To conclude, our findings reveal that HDR was associated with attenuated HRV and enhanced HEP during anticipation, and that the negative bias of HDR can be monitored by enhanced cardiac reactivity and HEP for unexpected negative stimuli. Moreover, HDR was the mediator of cardiac and neurophysiological responses for unexpected negative events. Altogether, neurophysiological processing of interoceptive prediction and prediction error under uncertainty and valence may be critical in HDR. The methods to assess such sensitivity of brain-heart interactions may be novel *neurocardiac* markers for depressive risk.

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Author Notes

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Tables

Table 1 Comparison of the non-HDR and HDR groups and correlation with BDI for mean HR changes during 5.4–10.7 s. *t* values are results of two-sample *t* tests, and *r* values are partial correlation coefficients controlling for age and sex.

Condition	HR changes (bpm)		Group comparison			Correlation to BDI		
	non-HDR group	HDR group	*t*	*p*	Hedges'g	*r*	*p*	r^2
PP	–1.30 (0.96)	–1.30 (0.40)	0.02	.983	0.01	–.14	.527	.018
UP	–0.86 (0.76)	–1.36 (0.98)	1.30	.239	0.59	–.17	.434	.028
XP	–1.08 (0.68)	–1.33 (0.56)	1.04	.366	0.38	–.19	.379	.035
PU	–1.51 (1.02)	–2.22 (0.70)	1.93	.075	0.75	–.21	.321	.045
UU	–1.28 (0.52)	–2.27 (0.31)	5.41	<.001*	2.08	–.61	.001*	.374
XU	–1.39 (0.60)	–2.24 (0.40)	3.86	<.001*	1.52	–.43	.034*	.188
PP – PU	0.21 (1.58)	0.91 (1.01)	–1.23	.229	–0.48	.08	.707	.007
UP – UU	0.42 (0.63)	0.92 (1.15)	–1.12	.293	–0.55	.43	.036*	.185
XP – XU	0.32 (0.82)	0.91 (1.77)	–1.75	.096	–0.74	.28	.192	.076

*: uncorrected $p < .05$; mean (*SD*)

Table 2 Comparison of the non-HDR and HDR groups and correlation with BDI for mean HRV changes during 9.2–12.1 s. *t* values are results of two-sample *t* tests, and *r* values are partial correlation coefficients controlling for age and sex.

Condition	HRV changes (ms)		Group comparison			Correlation to BDI		
	non-HDR group	HDR group	*t*	*p*	Hedges'g	*r*	*p*	r^2
PP	5.73 (7.35)	1.76 (7.24)	1.21	.244	0.52	–.34	.104	.116
UP	11.24 (11.72)	8.10 (9.89)	0.66	.519	0.27	–.31	.148	.093
PP – UP	–5.52 (7.13)	–6.34 (11.79)	0.18	.861	0.09	.08	.703	.007
PU	6.44 (8.60)	4.75 (6.17)	0.52	.607	0.21	–.21	.337	.042
UU	3.01 (6.26)	12.89 (10.79)	–2.36	.040*	-1.15	.38	.069	.143
PU – UU	3.43 (9.26)	–8.14 (6.14)	3.44	.003*	1.35	–.49	.016*	.238

*: uncorrected $p < .05$; mean (*SD*)

Table 3 Correlation between the pic – cue difference of HEP amplitude and BDI scores for each cluster. These *r* values are partial correlation coefficients controlling for age and sex.

Condition	HEP cluster 1			HEP cluster 2			HEP cluster 3		
	r	*p*	r^2	*r*	*p*	r^2	*r*	*p*	r^2
PP	–.04	.839	.002	.07	.746	.005	.24	.264	.056
PU	–.10	.656	.009	.03	.889	.001	.01	.955	.000
UP	.06	.781	.004	.14	.516	.019	–.13	.548	.017
UU	.30	.156	.089	–.12	.576	.014	–.56	.005*	.308

*: uncorrected $p < .01$

Table 4 Correlation between amplitude of the HEP and HR changes during 5.4–10.7 s for each cluster. These *r* values are partial correlation coefficients controlling for age and sex.

HEP phase	Condition	HEP cluster 1			HEP cluster 2			HEP cluster 3		
		r	*p*	r^2	*r*	*p*	r^2	*r*	*p*	r^2
cue	PP	–.21	.321	.045	–.03	.900	.001	.07	.739	.005
	PU	.44	.033*	.190	–.01	.965	.000	–.27	.208	.071
	UP	.11	.602	.013	–.01	.563	.015	–.23	.282	.052
	UU	.34	.107	.114	–.38	.069	.143	–.40	.055	.158
pic	PP	–.40	.055	.158	.09	.673	.008	.11	.611	.012
	PU	.21	.333	.043	–.03	.888	.001	–.37	.079	.133
	UP	.36	.085	.129	–.32	.126	.103	–.09	.677	.008
	UU	.44	.030*	.197	–.55	.005*	.305	–.27	.210	.070

*: uncorrected $p < .05$

Figure captions

Figure 1 Time series of heart rate (HR) changes in four conditions, PP, PU, UP, and UU in (a) all participants, (b) the non-HDR group, and (c) the HDR group. The gray-shaded area indicates the time period showing the significant main effect of emotional picture in the cue × pic RM-ANOVA analysis and horizontal lines represent the period showing a significant difference in paired *t*-tests ($p_{\text{FDR-corrected}} < .05$ and duration > 1 s). The left and right vertical dashed lines indicate the onsets of cue and picture presentation, respectively. Red and blue shaded areas along the HR time series represent one standard error. HDR: high depressive risk; PP: predictable pleasant; PU: predictable unpleasant; UP: unpredictable pleasant; UU: unpredictable unpleasant.

Figure 2 (a) Effect of cue and (b) effect of picture on changes in heart rate (HR). Error bars represent 1.96 within-subject standard errors and asterisks (*) denote the presence of significant main effects of stage (anticipation vs. perception) and condition (cues or valence) in 2 × 2 RM-ANOVA analysis ($p < .05$). (c) Partial correlation (*r*) between HR changes at *perception* stage (5.4–10.7 s) and level of HDR (BDI scores), controlled for age and gender. Asterisks (*) denote the presence of a significant partial correlation ($p < .05$). Each circle denotes one participant and solid lines are linear fitted trend lines. HDR: high depressive risk; PP: predictable pleasant; PU: predictable unpleasant; UP: unpredictable pleasant; UU: unpredictable unpleasant; *n.s.*: not significant.

Figure 3 Time courses of heart rate variability (HRV) in the four conditions PP, PU, UP, and UU for (a) all participants, (b) non-HDR group, and (c) HDR group. The grey shaded area indicates the duration showing the significant main effect of *cue* in the cue x pic RM-ANOVA analysis and horizontal lines represent the duration showing a significant effect in paired *t*-tests ($p_{\text{uncorrected}} < .05$ and duration > 1 s). The left and right vertical dashed lines indicate the onsets of cue and picture presentation, respectively. Red and blue shaded areas along the HRV time series represent one standard error. HDR: high depressive risk; PP: predictable pleasant; PU: predictable unpleasant; UP: unpredictable pleasant; UU: unpredictable unpleasant; UX: unpredictable condition regardless of valence of pictures.

Figure 4 (a) Effects of cue and (b) of picture on changes of heart rate variability (HRV). Error bars represent 1.96 within-subject standard errors and asterisks (*) denote the presence of significant main effects of stage (anticipation vs. perception) and condition (cues or valence) in 2 × 2 RM-ANOVA analysis ($p < .05$). (c) Partial correlation (r) between HRV changes at *anticipation* stage (1.5–4 s) and level of HDR (BDI scores) controlled for age and gender. Asterisks (*) denote the presence of significant partial correlation ($p < .05$). Each circle denotes one participant and solid lines are the linear fitted trend lines. PP: predictable pleasant; PU: predictable unpleasant; UP: unpredictable pleasant; UU: unpredictable unpleasant; *n.s.*: not significant.

Figure 5 (a) Grand average of original heartbeat-evoked potential (HEP), obtained via epoching EEG signals based on actual R peaks, and surrogate HEP, obtained via epoching EEG signals based on randomly-shifted R peaks, during –0.1 to 0.6 s. The scalp distribution of HEP is viewed from above. (b) Blue squares, green triangles, and red circles indicate channel positions of HEP clusters 1, 2, and 3 determined by the spatiotemporal nonparametric cluster-level test over the time series of HEP and surrogate HEP during 0.1–0.6 s. Significant durations for HEP clusters 1, 2, and 3 are 0.10–0.40 s, 0.10–0.29 s, 0.23–0.37 s, respectively.

Figure 6 Boxplots of (a) heartbeat-evoked potential (HEP) amplitude for HEP clusters 1, 2, and 3 and amplitude *difference* for HEP clusters 1, 2, and 3 (b) between picture- and cue- phases (picture – cue) across all four conditions, (c) between predictable and unpredictable conditions, and (d) between pleasant and unpleasant conditions reflecting the effect of valence, reflecting the effect of certainty. White (left) and gray (right) boxes represent non-HDR and HDR groups, respectively. The horizontal bars connecting two bars indicate significantly different conditions between non-HDR and HDR groups in two-sample t tests. *: FDR-corrected $p < .05$. HDR: high depressive risk; PP: predictable pleasant; PU: predictable unpleasant; UP: unpredictable pleasant; UU: unpredictable unpleasant.

Figure 7 Heartbeat-evoked potential (HEP) averaged over channels of the right frontotemporal cluster (cluster 3) for (a) PP, (b) PU, (c) UP, and (d) UU conditions. Dashed lines represent the picture-phase and solid lines represent the cue-phase. The gray shaded area along HEP waveforms represents one standard error. Gray rectangles indicate a significantly different time-window, 0.23–0.37 s, between the HEP and the surrogate HEP in the cluster-based spatiotemporal permutation test. The asterisk (*) indicates the significantly different effect of the HEP difference between the non-HDR and HDR groups (two-sample *t*-tests FDR-corrected $p < .05$). HDR: high depressive risk; PP: predictable pleasant; PU: predictable unpleasant; UP: unpredictable pleasant; UU: unpredictable unpleasant.

Figure 8 Grand averaged heartbeat-evoked potential (HEP) of the non-HDR and HDR groups plotted as a function of time for cluster 3 at cue phase. Dashed lines represent pleasant conditions and solid lines represent unpleasant conditions. The gray shaded area along the HEP waveform represents one standard error. The gray rectangle indicates the time period showing a significant difference between the grand averaged HEP and the surrogate HEP for cluster 3 in cluster-based spatiotemporal permutation test. The asterisk (*) indicates that the difference of the valence effect of HEP between the non-HDR and HDR groups exceeded FDR-corrected $p < .05$ in two-sample *t*-tests, respectively. HDR: high depressive risk.

Figure 9 Models to predict changes of heart rate (HR) under the unpredictable unpleasant (UU) condition from (a) the heartbeat evoked potential (HEP) of cluster 3 at *cue phase* and (b) the difference of HEP amplitude between pic phase and cue phase (*pic – cue diff*) in cluster 3 mediated by HDR, which is quantified using a BDI score. *: $p < .05$. HDR: high depressive risk.

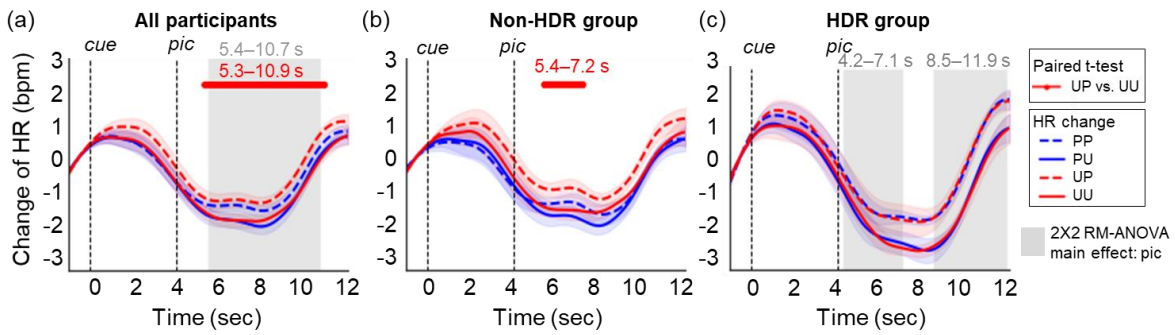
(a)
All participants
cue
pic
5.4–10.7 s
5.3–10.9 s
Change of HR (bpm)
Time (sec)
(b)
Non-HDR group
cue
pic
5.4–7.2 s
Time (sec)
(c)
HDR group
cue
pic
4.2–7.1 s
8.5–11.9 s
Time (sec)
Paired t-test
UP vs. UU
HR change
PP
PU
UP
UU
2X2 RM-ANOVA
main effect: pic

Figure 1

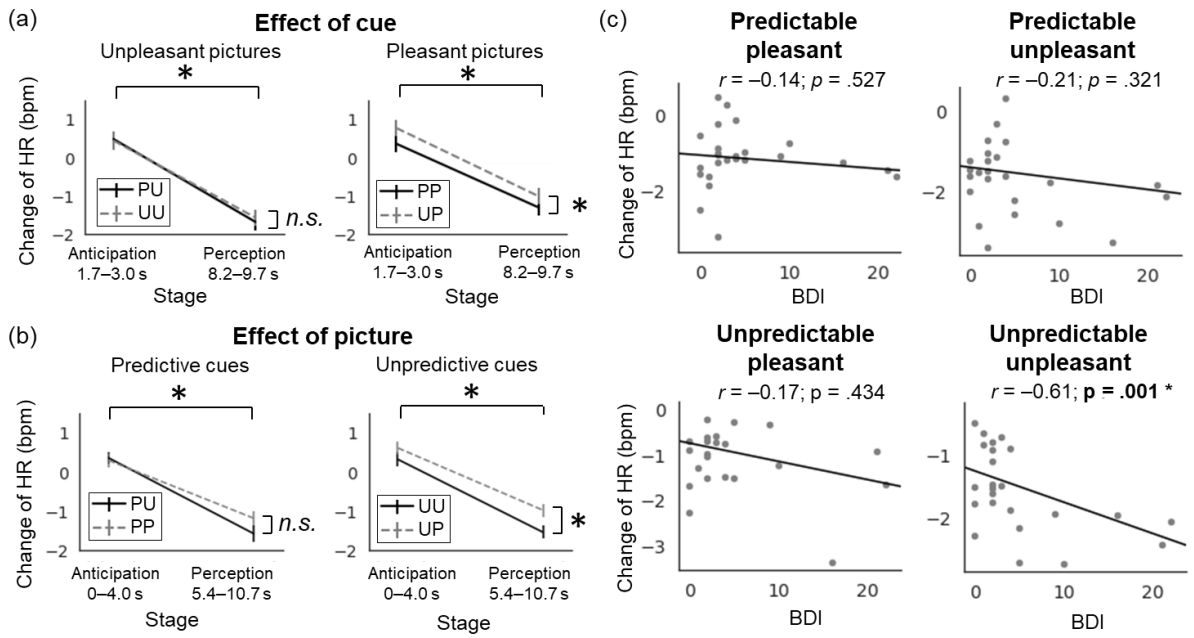
(a)
Effect of cue
Unpleasant pictures
Pleasant pictures
Change of HR (bpm)
PU
UU
PP
UP
n.s.
Anticipation
1.7–3.0 s
Perception
8.2–9.7 s
Stage
(b)
Effect of picture
Predictive cues
Unpredictive cues
Anticipation
0–4.0 s
Perception
5.4–10.7 s
(c)
Predictable pleasant
r = –0.14; p = .527
Predictable unpleasant
r = –0.21; p = .321
Unpredictable pleasant
r = –0.17; p = .434
Unpredictable unpleasant
r = –0.61; p = .001 *
BDI

Figure 2

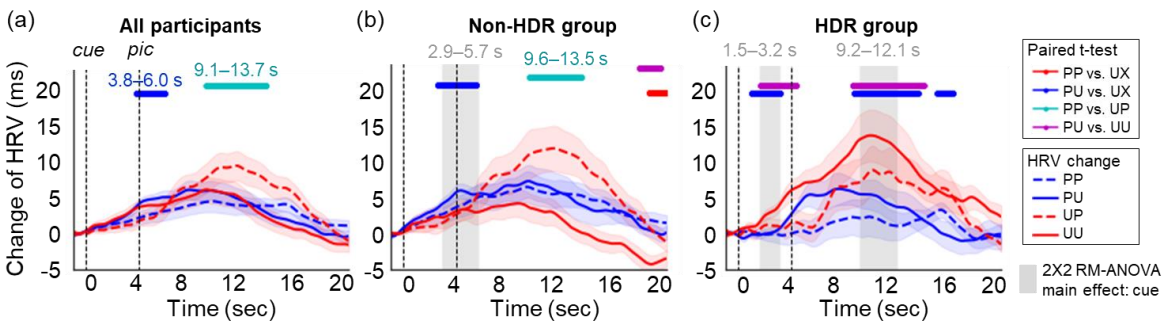
(a)
All participants
cue
pic
3.8–6.0 s
9.1–13.7 s
Change of HRV (ms)
Time (sec)
(b)
Non-HDR group
2.9–5.7 s
9.6–13.5 s
Time (sec)
(c)
HDR group
1.5–3.2 s
9.2–12.1 s
Time (sec)
Paired t-test
PP vs. UX
PU vs. UX
PP vs. UP
PU vs. UU
HRV change
PP
PU
UP
UU
2X2 RM-ANOVA
main effect: cue

Figure 3

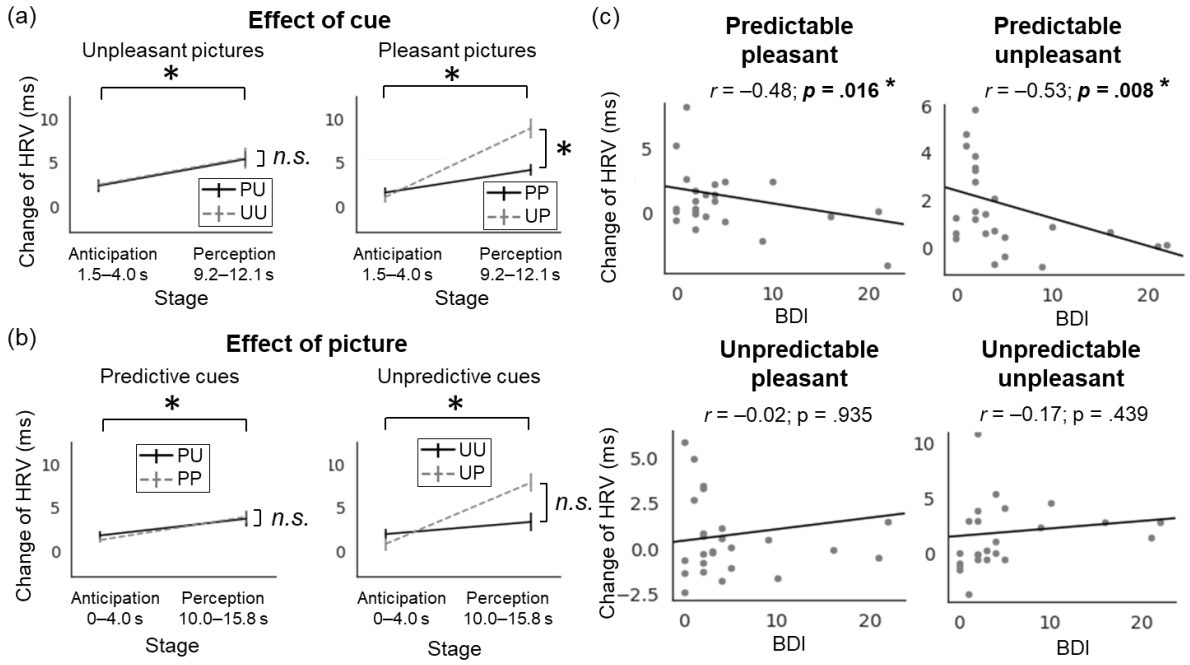
(a)
Effect of cue
Unpleasant pictures
Pleasant pictures
Change of HRV (ms)
PU
UU
PP
UP
n.s.
Anticipation 1.5–4.0 s
Perception 9.2–12.1 s
Stage
(b)
Effect of picture
Predictive cues
Unpredictive cues
Anticipation 0–4.0 s
Perception 10.0–15.8 s
(c)
Predictable pleasant
r = –0.48; p = .016 *
Predictable unpleasant
r = –0.53; p = .008 *
Unpredictable pleasant
r = –0.02; p = .935
Unpredictable unpleasant
r = –0.17; p = .439
BDI

Figure 4

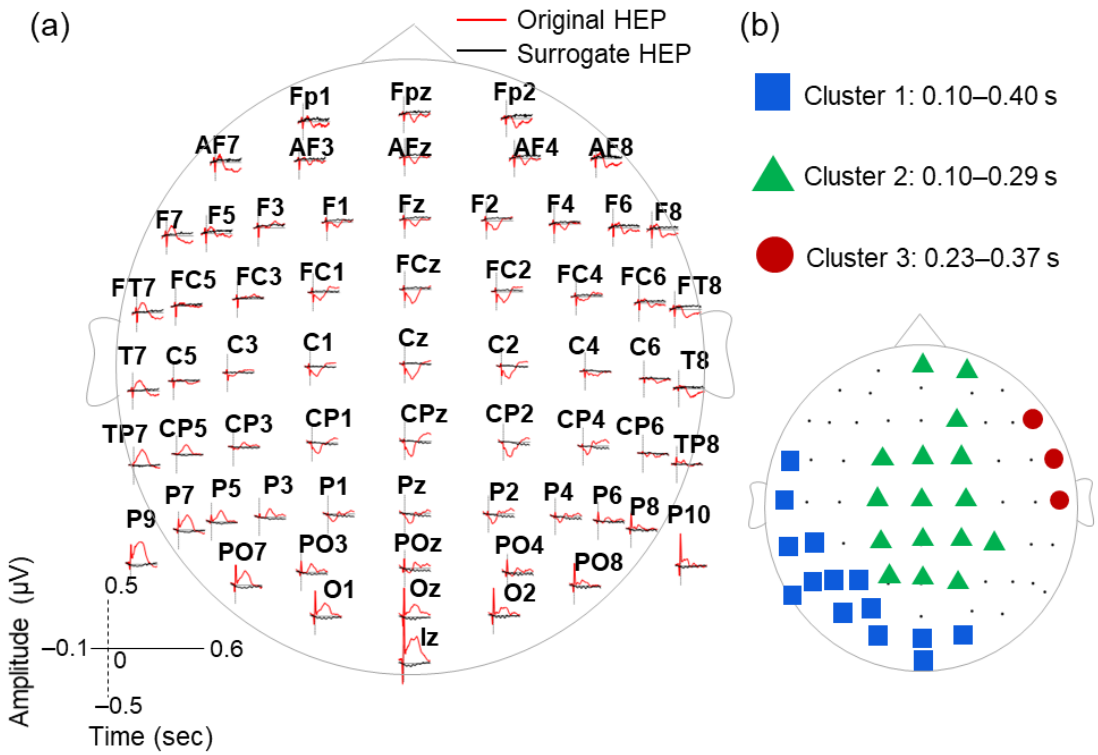
(a)
Original HEP
Surrogate HEP
Fp1
Fpz
Fp2
AF7
AF3
AFz
AF4
AF8
F7
F5
F3
F1
Fz
F2
F4
F6
F8
FT7
FC5
FC3
FC1
FCz
FC2
FC4
FC6
FT8
T7
C5
C3
C1
Cz
C2
C4
C6
T8
TP7
CP5
CP3
CP1
CPz
CP2
CP4
CP6
TP8
P9
P7
P5
P3
P1
Pz
P2
P4
P6
P8
P10
PO7
PO3
POz
PO4
PO8
O1
Oz
O2
Iz
0.5
−0.1
0
0.6
−0.5
Amplitude (μV)
Time (sec)
(b)
Cluster 1: 0.10–0.40 s
Cluster 2: 0.10–0.29 s
Cluster 3: 0.23–0.37 s

Figure 5

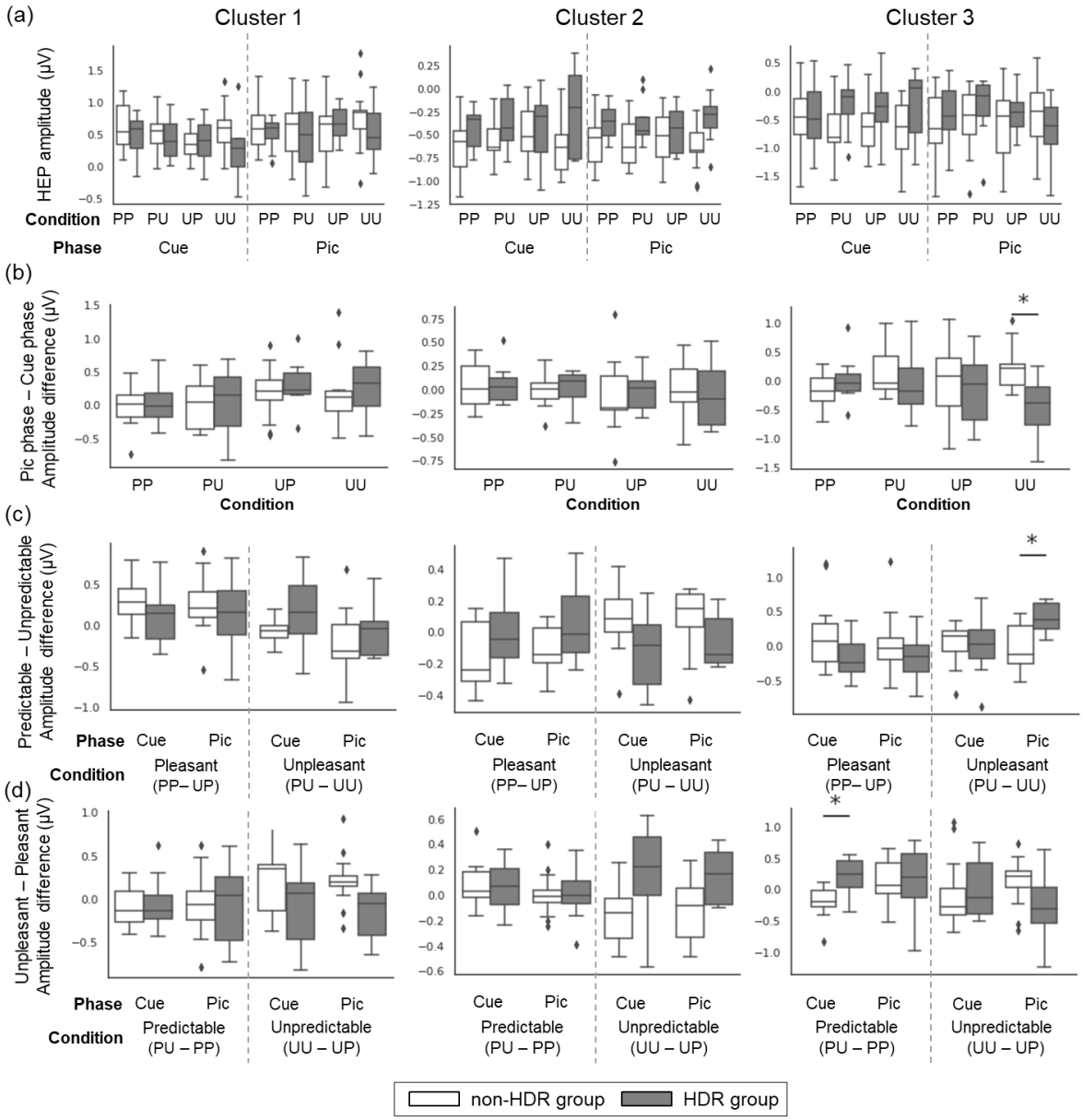
(a)
Cluster 1
Cluster 2
Cluster 3
HEP amplitude (μV)
Condition
PP PU UP UU PP PU UP UU
Phase
Cue
Pic
(b)
Pic phase – Cue phase Amplitude difference (μV)
PP PU UP UU
Condition
(c)
Predictable – Unpredictable Amplitude difference (μV)
Phase Cue Pic Cue Pic
Condition
Pleasant (PP– UP)
Unpleasant (PU – UU)
(d)
Unpleasant – Pleasant Amplitude difference (μV)
Phase Cue Pic Cue Pic
Condition
Predictable (PU – PP)
Unpredictable (UU – UP)
non-HDR group
HDR group

Figure 6

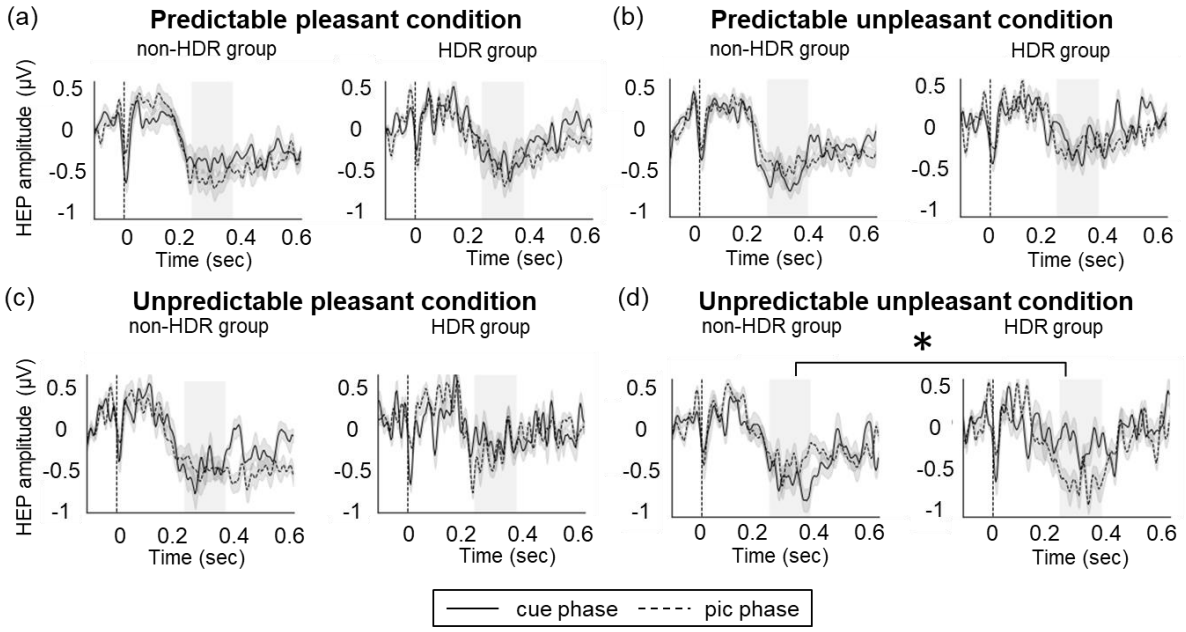
(a)
Predictable pleasant condition
non-HDR group
HDR group
(b)
Predictable unpleasant condition
non-HDR group
HDR group
(c)
Unpredictable pleasant condition
non-HDR group
HDR group
(d)
Unpredictable unpleasant condition
non-HDR group
HDR group
*
HEP amplitude (μV)
0.5
0
-0.5
-1
0
0.2
0.4
0.6
Time (sec)
cue phase
pic phase

Figure 7

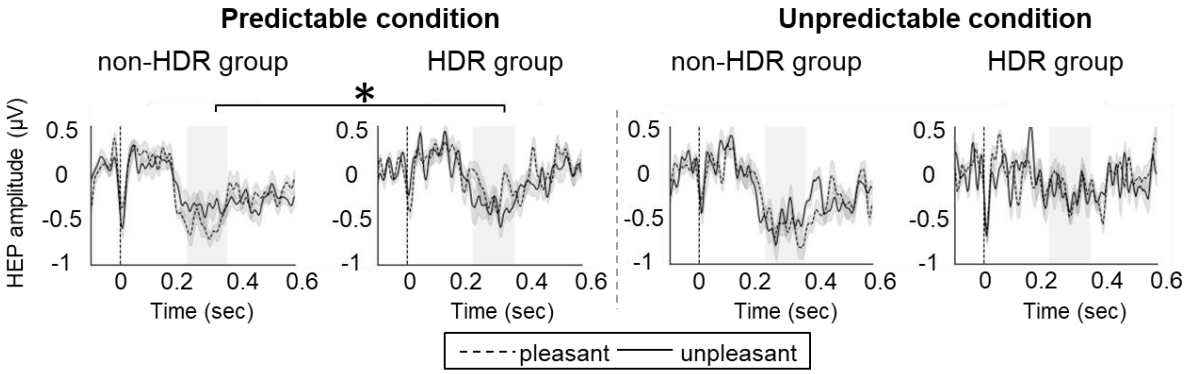
Predictable condition
Unpredictable condition
non-HDR group
HDR group
non-HDR group
HDR group
*
HEP amplitude (μV)
0.5
0
-0.5
-1
0
0.2
0.4
0.6
Time (sec)
pleasant
unpleasant

Figure 8

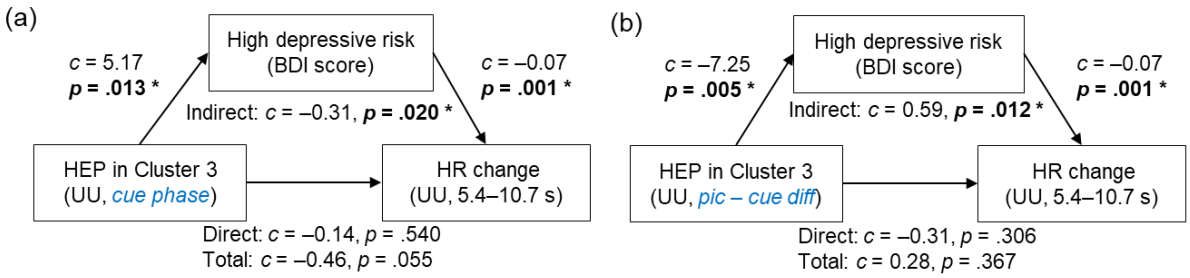
(a)
High depressive risk
(BDI score)
c = 5.17
p = .013 *
c = –0.07
p = .001 *
Indirect: c = –0.31, p = .020 *
HEP in Cluster 3
(UU, cue phase)
HR change
(UU, 5.4–10.7 s)
Direct: c = –0.14, p = .540
Total: c = –0.46, p = .055
(b)
High depressive risk
(BDI score)
c = –7.25
p = .005 *
c = –0.07
p = .001 *
Indirect: c = 0.59, p = .012 *
HEP in Cluster 3
(UU, pic – cue diff)
HR change
(UU, 5.4–10.7 s)
Direct: c = –0.31, p = .306
Total: c = 0.28, p = .367

Figure 9