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From the inside out: Interoceptive feedback facilitates the integration of visceral signals for efficient sensory processing

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ABSTRACT

Neuroscientific studies have mainly focused on the way humans perceive and interact with the external world. Recent work in the interoceptive domain indicates that the brain predictively models information from inside the body such as the heartbeat and that the efficiency with which this is executed can have implications for exteroceptive processing. However, to date direct evidence underpinning these hypotheses is lacking. Here, we show how the brain predictively refines neural resources to process afferent cardiac feedback and uses these interoceptive cues to enable more efficient processing of external sensory information. Participants completed a repetition-suppression paradigm consisting of a neutral repeating face. During the first face presentation, they heard auditory feedback of their heartbeat which either coincided with the systole of the cardiac cycle, the time at which cardiac events are registered by the brain or the diastole during which the brain receives no internal cardiac feedback. We used electroencephalography to measure the heartbeat evoked potential (HEP) as well as auditory (AEP) and visual evoked potentials (VEP). Exteroceptive cardiac feedback which coincided with the systole produced significantly higher HEP amplitudes relative to feedback timed to the diastole. Elevation of the HEP in this condition was followed by significant suppression of the VEP in response to the repeated neutral face and a stepwise decrease of AEP amplitude to repeated heartbeat feedback. Our results hereby show that exteroceptive heartbeat feedback coinciding with interoceptive signals at systole enhanced interoceptive cardiac processing. Furthermore, the same cue facilitating interoceptive integration enabled efficient suppression of a visual stimulus, as well as repetition suppression of the AEP across successive auditory heartbeat feedback. Our findings provide evidence that the alignment of external to internal signals can enhance the efficiency of interoceptive processing and that cues facilitating this process in either domain have beneficial effects for internal as well as external sensory processing.

1. Introduction

The human body is the seat of our self-awareness. Simultaneously, it is our primary instrument for experiencing and interacting with the world around us. It therefore comes as no surprise that research on interoception has progressed from studying the differences between external and internal sources of self-relevant information (Seth, 2013; Apps and Tsakiris, 2014) towards investigating the integration of both signals for a holistic experience of our self as an individual and agent within the external world.

Recent studies have explored the integrated processing of intero- and exteroceptive information by using biofeedback (i.e. stimuli coinciding with ongoing visceral afferent signals) to combine external and bodily cues into a multi-sensory simulation. The majority of this work focuses on cardiac information, linking audio or visual cues to certain phases of the cardiac cycle (i.e. the ventricular systole or diastole of the heartbeat). The different phases of the cardiac cycle are produced by the contraction of the heart muscle. During systole, chambers of the heart muscle contract, pumping blood from the heart to the body. Signals of this contraction are picked up by arterial baroreceptors which are located in the carotid arteries and in the aorta and convey the heart's movement to the brain, thereby allowing it to sense blood flow and blood pressure. At diastole, the heart muscle is relaxed as it refills with blood and no baroreceptor signals are sent to the brain. In terms of interoception, cardiac signals furthering interoceptive processing of the heartbeat are thus only transmitted during systole. Studies utilising the different cardiac phases report an effect of intero- and exteroceptive alignment on sensory experience, suggesting that systole alignment can alter perceptual sensitivity towards visual and cardiac signals and dampen sensory experience of stimuli such as pain. Specifically, heartbeat biofeedback at systole has been found to increase the expression of the heartbeat evoked potential (HEP) (Suzuki, Garfinkel, Critchley and Seth, 2013; Sel et al., 2017), a widely used EEG-measure of cortical heartbeat processing. Al and colleagues (2020.; 2021) reported that an increase of HEP amplitude coincides with reduced localisation and detection of an electrical finger pulse as well as the reduction of late sensory evoked potentials, an effect

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which was exacerbated if the finger pulse was delivered during cardiac systole. Wilkinson and colleagues (2013) tested pain perception of electrocutaneous stimuli, observing higher pain thresholds for stimuli delivered during systole. Similarly, Gray and colleagues (2010) demonstrated that expectancy evoked amplification of the pain induced P2 component was negated if the painful stimulus coincided with the cardiac systole.

Past work investigating the influence of the cardiac cycle on perceptual awareness in the visual (Elliot & Graf, 1972) and auditory domain (Velden & Juris, 1975) failed to find any effect. However, more recent evidence highlights that the cardiac phase has a significant impact on visual processing. For example, visual information gathering has been found to occur during systole (Galvez-Pol, McConnell and Kilner, 2020). To this effect, Garfinkel and colleagues (2014) demonstrated that fearful faces presented at the threshold of conscious detection were more readily perceived and rated as more intense if presented at systole, while Pramme and colleagues (2016) report that visual selection efficiency is enhanced for cues presented at systole. Conversely, visual awareness for stimuli coupled to the diastole is suppressed relative to stimuli presented asynchronously to the heartbeat (Salomon et al., 2016).

Evidence thus highlights that the processing of interoceptive signals can have a perceptible influence on the exteroceptive domain, which has led to the suggestion that intero- and exteroceptive processing may be allocated within a joint framework of sensory processing based on the principles of predictive coding (Seth et al., 2013; Marshall et al., 2018a; Gentsch et al., 2019 ; Owens et al., 2018). According to this account, the brain generates predictions about sensory sources and outcome states across different hierarchical levels and several sensory and motor domains. Descending predictions are compared to ascending sensory inputs to generate prediction errors, discrepancies which the brain seeks to minimise by adjusting its priors or by initiating actions that alter sensory input. Work exploring the predictive nature of interoceptive processing has shown that repeating an affective visual stimulus can enhance predictive interoceptive integration: the heartbeat pattern elicited by the first stimulus is used as a prior to refine cognitive resources and more efficiently process heartbeat information in response to the successive stimuli. In line with this, repetition of the same facial expression has been shown to produce highly similar heartbeat patterns (interbeat intervals), whereas alternating expressions cause significant discrepancies between interbeat intervals generated in response to the different presented emotions (Marshall et al., 2018b). Repeated expressions have further been shown to modulate the heartbeat evoked potential and visual evoked potentials elicited by viewing the visual stimulus (Summerfield et al., 2011; Marshall et al., 2017), thereby highlighting that stimulus predictability affects both intero- and exteroceptive processing domains. In addition, we observed that repetition of neutral expressions increased HEP amplitude while repetition of angry faces decreased it (Marshall et al., 2018b). This HEP modulation as a function of stimulus relevance for internal versus external surroundings suggests our brain can preferentially allocate resources if the situational demands of one domain exceed those of the other. To date, the above-mentioned HEP effects have been elicited indirectly, using affective stimuli that were presented on a computer screen, for example, to modulate heartbeat patterns. Despite these studies suggesting a causal interplay between interoceptive and exteroceptive predictions, direct evidence has not been provided yet and the underlying dynamics are still poorly understood. An important development thus lies in using more direct means of interoceptive manipulations to allow stronger, more causal conclusions of the effects at play.

In this experiment, we use a repetition-suppression paradigm which has been successfully used for studying sensory predictions: participants encounter a face stimulus that is either repeated or changed, thereby matching or violating prior expectations. Here, we paired this paradigm with auditory biofeedback to directly manipulate interoceptive processing of the prior generated while viewing the first face of the trial sequence. During the first stimulus iteration, participants heard five tones linked to the systole or diastole of their own heartbeat. At systole (ventricular ejection period) heartbeat feedback coincided with the signalling of arterial baroreceptors in the brainstem, creating a unified experience of interoceptive and exteroceptive heartbeat feedback. Conversely at diastole, feedback was misaligned and did not correspond to interoceptive cardiac signals. We hypothesised that this misalignment with the formation of the heartbeat prior would inhibit interoceptive processing. Conversely, we expected interoceptive integration to be enhanced by systole biofeedback. Based on past research which reports elevated HEP amplitudes during contingent biofeedback (Suzuki et al., 2013), we expected significantly higher HEP amplitudes in the systole relative to the diastole feedback condition. Based on results suggesting that enhanced interoceptive integration aids exteroceptive perception (Marshall et al., 2018b; Marshall et al., 2019), we further hypothesised the refinement of neural resources for external domains in the systole condition as reflected by repetition-suppression effects of both visual (VEP) and auditory evoked potentials (AEP). We expected no such modulation for diastole feedback.

2. Materials and method

2.1. Participants

Twenty-three healthy volunteers took part in the study (12 females, age 25.8 ± 3.9 y [mean ± SD], range: 19 to 34 y). We screened participants for state and trait anxiety (Spielberger et al., 1983), and depression (Beck et al., 1961) as both have been linked to altered interoceptive processing (Pollatos et al., 2009). All participants scored within the normal range.

2.2. Ethics statement

Procedures were approved by the ethics committee of the Ludwig-Maximilians University Munich in accordance with the Declaration of Helsinki (BMF 1991; 302; 1194). All participants gave informed consent and were compensated for their participation.

2.3. Procedure and task design

Participants completed a repetition-suppression paradigm in which a facial expression was presented twice within one trial and paired with heartbeat feedback (see Fig. 1). Stimuli were taken from the NimStim set of facial expressions (Tottenham et al., 2009) and included 40 young actors (20 females) modelling a neutral expression. The paradigm had three conditions. While viewing the first face, participants received auditory heartbeat feedback linked either to the systole (1) or the diastole (2) of their recorded ECG signal. In the third condition, we presented no heartbeat feedback while participants watched the first face. Cardiac feedback was presented for the duration of five heartbeats (= 5 tones). In each of the conditions, the first face was presented until five heartbeats were recorded. Timings of this stimulus thus varied according to participants' individual heartbeat signal and lasted between 4.5 to 5 s. Sound stimuli were 1000 Hz sinusoidal tones of 100 ms duration. They were presented binaurally via in-ear phones at approximately 70 dB loudness (individually adjusted). To synchronise the tone with specific cardiac timings we interfaced ECG signals with the task using RecView (Brain Vision GmbH). Based on past research, the tone for systole feedback was delivered to coincide with the T-wave peak at 290 ms after the peak of the R-wave (Park et al., 2014; Rae et al., 2019; Garfinkel and Critchley, 2016). For diastole feedback, the tone was delivered to coincide with the onset of the R-wave peak (Salomon et al., 2016). The experiment comprised 420 trials (140 trials per condition) and was divided into six blocks of 70 trials. Blocks were pseudo-randomised between participants. To ensure potential biofeedback effects had enough time to manifest each of the three conditions had two blocks which included only trials from one condition. Blocks belonging to the same condition were presented successively. However, the order of the conditions was

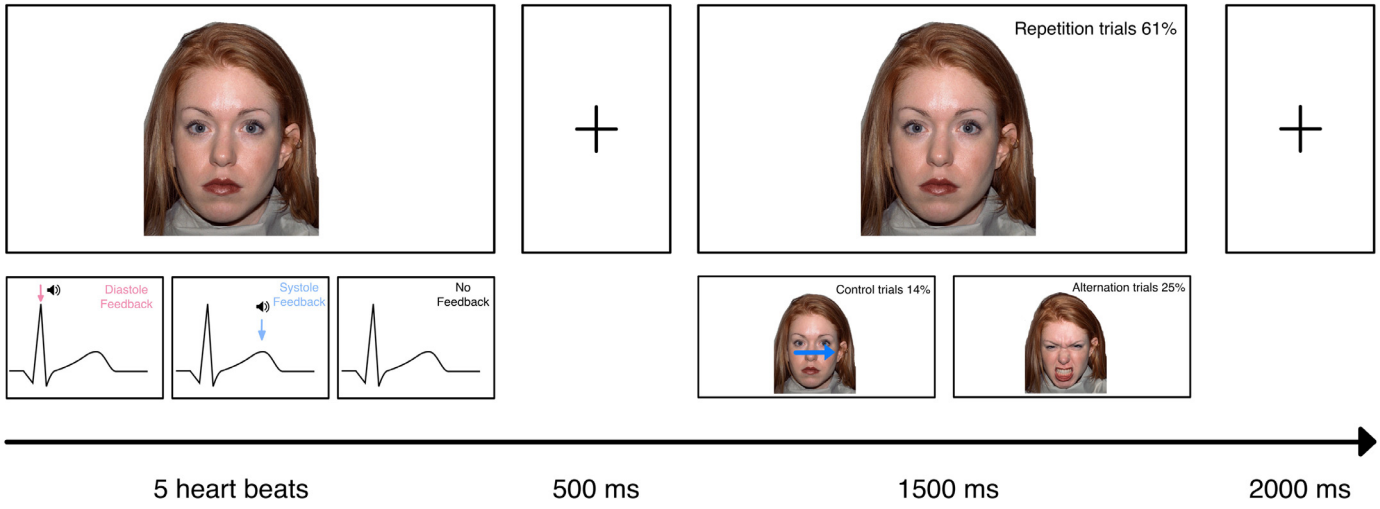

Fig. 1. Schematic representation of the biofeedback paradigm depicting the timeline and the different conditions. During the first face presentation participants received no cardiac biofeedback for 1/3rd of all trials. For the remaining 2/3rd of trials feedback was locked either to the diastole or the systole of the ECG signal. For most trials (61%) the second face consisted of a repetition of the same neutral expression. In a quarter of all trials the second face was alternated with an angry expression. The remaining trials were control trials in which participants needed to react via button press to an arrow superimposed on the second face.

randomised between participants. Ten trials of each block were control trials in which a blue arrow appeared superimposed on the second face. Participants were naïve to the experimental manipulation, as suggested by informal verbal inquiry about the purpose of the experiment after completion. They were told their task was to look for blue arrows which were superimposed on the second face and to press a button corresponding to the arrow's direction whenever one appeared. These control trials appeared at a rate of 14% (10 trials per block) and were used to ensure participants' continued attention. They were excluded from later EEG analysis. Participants completed 15 practice trials before moving on to the main experiment.

2.4. ECG recording and processing

The ECG signal was recorded at the rate of 500 Hz from two bipolar electrodes placed below the left clavicle and right pectoral muscle. The ground electrode was positioned below the right clavicle. Using Fieldtrip, ECG data were offline band-pass filtered between 1 and 40 Hz (basic finite impulse response filter, Hamming windowed). R-peaks for segmentation were calculated with the Pan-Tompkins algorithm (Pan and Tompkins 1985), implemented in Matlab. The timings of the R-peak, T-wave peak as well as the onset and offset of the T-wave in each trial were identified with the NeuroKit2 toolbox (Makowski et al., 2021) implemented in Python.

2.5. EEG recording and processing

EEG was recorded from 64 active electrodes (BrainProducts, ActiSnap) and one additional ground electrode, positioned according to the international extended 10-20 system. Data was recorded at a sampling rate of 500 Hz. The FCz electrode was used as an online reference. Using Fieldtrip, offline data were filtered (high-pass: 0.1 Hz, low-pass: 40 Hz) and re-referenced to the average of all electrodes. We then performed independent component analysis (ICA) to identify and remove components unrelated to neural activity, such as blinks or the cardiac field artefact (CFA), an electrical field produced by the contraction of the heart-muscle (Dirlich et al., 1997; Kern et al., 2013; Buot et al., 2021). To accurately identify the CFA, we computed the coherence between the ECG and the expression and time course of each component. We then produced an output of the topography, time course and average expression of the four components showing the highest symmetry to the ECG signal. We visually inspected each output and removed the components with a time-course and topography matching the CFA (Kaiser et al., 2021). This led to an average exclusion of 2.3 components across participants related to the CFA.

In this experiment, we presented auditory events linked to the R-peak of the electrocardiogram. Due to this, both auditory and heartbeat evoked potentials were time-locked to the same event and both had a high coherence with the time-course of the ECG. To ensure that auditory and heartbeat evoked components did not infringe upon one another, we used the same procedure for identification and deletion of the CFA to extract auditory and heartbeat potentials. To delete the AEP, we investigated the first 30 components showing the highest coherence to the ECG signal and searched for distinct components displaying the frontal topography reported for potentials related to auditory orienting responses (Wronka, Kaiser and Coenen, 2012). This led to the average identification of 2.5 components. For the HEP, we investigated the first 30 components displaying the highest coherence to the ECG signal. We searched for distinct components manifesting across the vertex whose shape matched the flattened curve of the generally reported HEP (Canales-Johnson et al., 2015; Couto et al., 2014). This led to an average identification of 1.7 components. We then created two datasets. We removed components whose topography and time course matched auditory events from the dataset used to analyse the HEP and conversely removed the HEP from the data used to analyse the AEP (see supplementary Figures 1 a and 2 a). To test whether exclusion of the relative components was successful, we extracted the grand average waveforms from each dataset. For the dataset from which the AEP was deleted, we segmented the data from 0 – 600 ms after the tone onset. For the dataset from which the HEP was deleted, we segmented data from 0 – 1000 ms after the R-peak marker. We then calculated the grand average waveform across all participants and electrodes. We proceeded with the primary analysis once each grand average wave showed no residual AEP and HEP activity.

We extracted AEP activity corresponding to the first four tones of auditory heartbeat feedback. We excluded the fifth tone as we could not ensure that the complete time window did not carry over into the inter-stimulus-interval (ITI). For diastole feedback, we segmented the data from -100 to 1000 ms around the first four R-peak markers. For systole feedback, we segmented 190 to 1290 ms around the first four R-peak markers. In both cases, we used the first 100 ms for baseline correction. For the HEP, we segmented the data from -100 to 1000 ms

around the first four R-peak markers, using the 100 ms prior to the R-peak for baseline correction. We again excluded the fifth heartbeat. We further extracted activity during the inter-trial-interval succeeding presentation of the second face. Data was segmented from -100 to 1000 ms around the first R-peak marker following the onset of the ITI, again using the 100 ms prior to onset of the R-peak for baseline correction. We extracted VEP activity in response to viewing the second face of the repetition-suppression paradigm. For this, we segmented the data from -100 to 1000 ms from the onset of the second face marker, using the -100 ms before the face appeared for baseline correction. After segmentation, we removed all segments in which activity exceeded ± 100 μV which led to an average exclusion rate of 2.37% (SD = 2.99), thus retaining on average 135 trials per condition.

2.6. Statistical analysis

We determined ERP morphology and time windows of interest using a mass univariate, cluster-based permutation procedure following the principles described in Maris and Oostenveld (2007) and implemented in Fieldtrip. EEG data for the segmented 0 – 1000 ms time window across all 64 electrodes was submitted to a repeated-measures, two-tailed permutation test. For each sample (2 ms time window occurring from the natural sampling of the data across each of the 64 electrodes), we identified neural phenomena that differed for the main effect of systolic vs. diastolic feedback and calculated point-estimate statistics (t-values obtained using dependent samples t-tests) associated with this main effect. Samples were clustered based on temporal and spatial adjacency (any electrodes within 5 cm of one another were considered spatial neighbours). Cluster-level statistics were calculated by taking the sum of t-values within each cluster and obtaining the test statistic largest in absolute value within each cluster.

Significance probability was calculated via the Monte-Carlo method. For this, we created two new datasets by shuffling trials between both conditions and calculated the maximal value of cluster summed t-values resulting from their comparison. We permuted the dataset in this fashion 10,000 times. Across each permutation, the maximal test-statistic was logged, providing a distribution of maximal values obtained under the null hypothesis. We determined the p-value by calculating the proportion of random comparisons that produced a larger test statistic than the one originally observed. We selected all samples whose maximal t-values exceeded the critical alpha level of 0.05 for subsequent analysis.

ERP amplitude and behavioural data obtained for control trials was analysed with a repeated measures ANOVA. For the first HEP component and the AEP extracted in response to the biofeedback the ANOVA included the factors FEEDBACK TYPE (systolic vs. diastolic vs. none) and TONE REPRESENTATION (1 vs. 2 vs. 3 vs. 4). For behavioural measures, the VEP and the second HEP component extracted in response to the repeated face, the ANOVA included FEEDBACK TYPE (systolic vs. diastolic vs. none). Results were Greenhouse Geisser corrected when necessary. Follow-up t-tests were Bonferroni corrected. We report η_p^2 and Cohen's d as effect sizes. In addition, we report Bayes Factors (BF), which estimate the ratio of evidence for the alternative hypothesis relative to evidence for the null hypothesis. Bayes Factors > 3 are seen as evidence for the alternative hypothesis. Conversely, BF < .033 are taken as evidence for the null hypothesis (Jarosz and Wiley, 2014). For the calculation of all tests, we used the R packages *ez, multcomp* and *BayesFactor*.

2.7. Control variables

We created surrogate R-peaks to test whether observed HEP modulation was a true measure of sequential cardiac processing across the different types of biofeedback (Park et al., 2016; . We generated 400 surrogate R-peaks per participant by randomly shifting the sequence of four heartbeats between trials. R-peaks were shifted separately for each subject and condition. We pre-processed this data with the same steps described above and submitted these surrogate values to our permutation analysis. Using the surrogate R-peaks, we again compared systolic and diastolic conditions across all 64 electrodes and time points across the 1000 ms time window of interest and logged the maximal statistic of each test. This generated a second control distribution of maximal statistics obtained using surrogate R-peaks. We then compared the original test values to this distribution to test whether the previously significant values still fell above the 95th percentile.

To test whether cognitive rather than physiological cardiac effects governed our HEP results we obtained peak R-wave and mean T-wave activity from the ECG signal during the ~ 5000 ms interval during which we presented heartbeat feedback and measured the HEP. After filtering and R-peak detection, data was loaded into Brain Vision Analyser and epoched from -150 to 150 ms around the R-peak and from 240 to 340 ms after the R-peak for R-peak and T-wave activity respectively. The Peak Information Export function was then used to extract the R-peak value within a ∓ 1 point interval around the peak. T-wave activity was exported using the area export function. In addition, we used the area export function to extract mean ECG wave amplitude in the time window of 300 – 500 ms after the R-peak during biofeedback presentation. This allowed us to test for potential differences to the ECG signal in the time window for which we expected primary HEP effects to occur.

We also wanted to test whether diastolic feedback produced higher homeostatic arousal which may have influenced cognitive processing of the heartbeat and visual stimulus at later stages of the experiment. For this, we measured interbeat intervals and heartbeat variability (quantified as the root mean square of successive R to R interval differences; RMSSD) in response to the first facial presentation. Cardiac parameters were calculated using the RHRV package (Rodríguez-Liñares, Vila, Mendez, Lado, and Olivieri, 2008) implemented in R. We also included a fourth condition (140 trials, presented in the same manner described above) in which we presented diastolic feedback and proceeded to alternate the facial repetition sequence by showing an angry instead of a neutral face for the 2nd face presentation. Angry facial expressions were also taken from the NimStim set of facial expressions (Tottenham et al., 2009). This allowed us to test whether an arousing alternation of an emotionally salient visual stimulus produced stronger effects than our true experimental manipulation.

3. Results

3.1. AEP to biofeedback

The permutation test returned a significant difference between systolic and diastolic feedback across the right frontal region (FP2, AF8, Fz, F2, F4, F6, F8; t = 6.133^{05}, p = .004) which manifested from 376 – 422 ms after tone onset. Analysis of this electrode cluster found a significant interaction between feedback type and tone representation [F(6,132) = 3.17, p = .008, η_P^2 = 0.12; BF = 1.2^{22}][1]. For systolic biofeedback, AEP amplitude systematically decreased across the four tone representations. This led to a significant difference between AEP amplitudes to the first (0.67 μV) and the third (0.38 μV) tone [t(22) = 4.45, p < .001, 95% CI [0.07, 0.52], Cohen's d = 0.63] as well as AEP amplitudes to the first (0.67 μV) and the fourth (0.41 μV) tone [t(22) = 3.98, p = .007, 95% CI [0.04, 0.49], Cohen's d = 0.65; see Figure 2c]. No such step-

[1] In the reported analysis the no-feedback condition (segmented -100 – 1000 ms) does not include the same cardiac events as the systole condition (segmented 190 – 1290 ms). To ensure that this difference did not produce spurious results, we re-calculated the ANOVA with the no-feedback condition segmented in the same period as the systole condition. Results reproduced the significant interaction between tone representation and feedback type [F(6,132) = 3.15, p = .008, η_P^2 = 0.12; BF = 1.2^{22}], as well as the same simple main effects (first vs. third tone (p < .001) and first vs. fourth tone (p < .007) for systole; third tone systole vs. third tone disastole (p < .001), fourth tone systole vs. fourth tone diastole (p < .001).

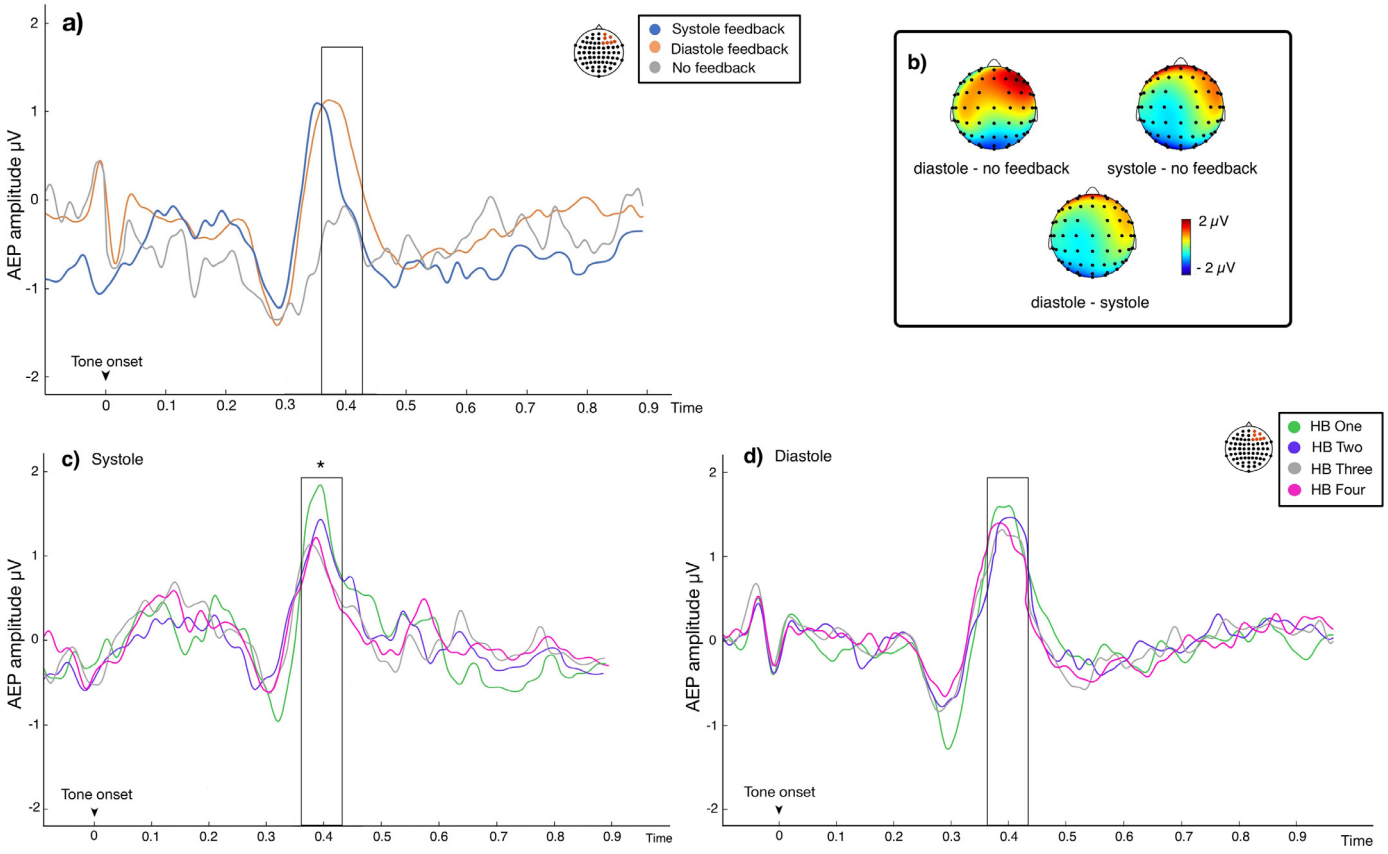

Fig. 2. AEP waveforms in response to the auditory cardiac biofeedback. **a)** AEP expression broken down by the different conditions. Uncorrected waveforms are shown in supplementary materials (Figure 1a).**b)** Topographies displaying the difference scores for the main effect of FEEDBACK TYPE **c)** AEP waveforms of the systole condition. Results showed a systematic decrease of amplitudes across the four auditory heartbeat representations. **d)** AEP waveforms for the diastole condition. Results found no decrease across the four auditory heartbeat representations.

wise decrease was observed for the AEP in response to no biofeedback [F(3,66) = 0.19, p = .91, $\eta_P^2 = 0.008$; BF = 0.072] and importantly we also observed none for diastolic biofeedback [F(3,66) = 0.79, p = .49, $\eta_P^2 = 0.035$; BF = 0.138]. Across conditions, this produced a significant difference between the systole and the diastole condition for the third [t(22) = 4.27, p < .001, 95% CI [0.07, 0.53], Cohen's d = 0.61] and fourth tone representation [t(22) = 4.96, p < .001, 95% CI [0.04, 0.38]. For later auditory heartbeat representations AEP, activity during systole feedback was significantly lower than corresponding activity in response to diastole feedback.

3.2. HEP to biofeedback

The permutation test revealed a significant difference between systolic and diastolic feedback for a time window of 318 to 494 ms after the R-peak marker across the vertex (FCz, Cz, FC2, C1, C2; t = 9.071^{07}, p = .003). Across this electrode cluster, we observed a main effect of feedback type [F(2,44) = 27,33, p < .001, $\eta_P^2 = 0.47$, BF > 5.7^{17}]. Biofeedback linked to the systole produced significantly higher HEP amplitudes (0.68 µV) compared to feedback linked to the diastole (-0.18 µV, p < .001) and no (0.13 µV, p < .001) heartbeat feedback (see Fig. 3). For the HEP, we found no effect of tone representation (all p_s > .05). As their effects manifested in the same time period, we ran a correlational analysis between HEP and AEP activity. This returned a weak negative association between both components (r_s = -.29, p = .036). Breaking this association down into the individual conditions revealed that this effect was most pronounced in the systole condition (r_s = -.31, p = .033), highlighting that for systole biofeedback, enhanced HEP amplitude during systole coincided with reduced AEP amplitude. Correlations did not reach significance for the diastole and no feedback conditions (p_s > .05).

3.3. VEP to the repeated face

Our permutation procedure returned a significant difference between systolic and diastolic feedback across frontal electrode sites (FP1, FP2, AF3, AFz, AF4; t = 8.004^{06}, p = .003) for a time window of 116 to 208 ms after the onset of the repeated face. This morphology suggests a P2 component. Analysis of this component found a main effect of feedback type [F(2,44) = 7.39, p = .003, $\eta_P^2 = 0.27$, BF = 10.08]. Post-hoc analysis of this effect showed that the repeated face following systolic biofeedback elicited significantly smaller VEP amplitudes (0.3 µV) compared to facial repetitions succeeding diastolic (0.82 µV) biofeedback [t(22) = -3.9, p = .004, 95% CI [-0.71, -0.13], Cohen's d = 0.68] and no (1.2 µV) biofeedback [t(22) = -5.8, p = .001, 95% CI [0.75, 1.39], Cohen's d = 0.83; see Fig. 4a]. Furthermore, the permutation test revealed a significant difference for systolic vs. diastolic feedback for a late time window around 600 to 700 ms after onset of the repeated face, suggesting a P600 component. This difference manifested across three areas of the scalp. We observed the first across left fronto-parietal electrode sites (FC5, FC3, T7, C5, C3, CP3; t = 4.062^{03}, p = .005) for a time window of 596 to 738 ms. Analysis of this electrode cluster revealed a main effect of feedback type [F(2,44) = 5.96, p = .005, $\eta_P^2 = 0.21$, BF = 9.65]. Post-hoc analysis of this effect found the repeated face elicited significantly reduced VEP amplitude if it succeeded systolic (0.2 µV) compared to diastolic (0.72 µV) heartbeat feedback [t(22) = -3.4, p = .004, 95% CI [-0.73, -0.11], Cohen's d = 0.71; see Fig. 4b]. The second region of interest manifested across right frontal electrodes (F6, FC4, FC6, FT8;

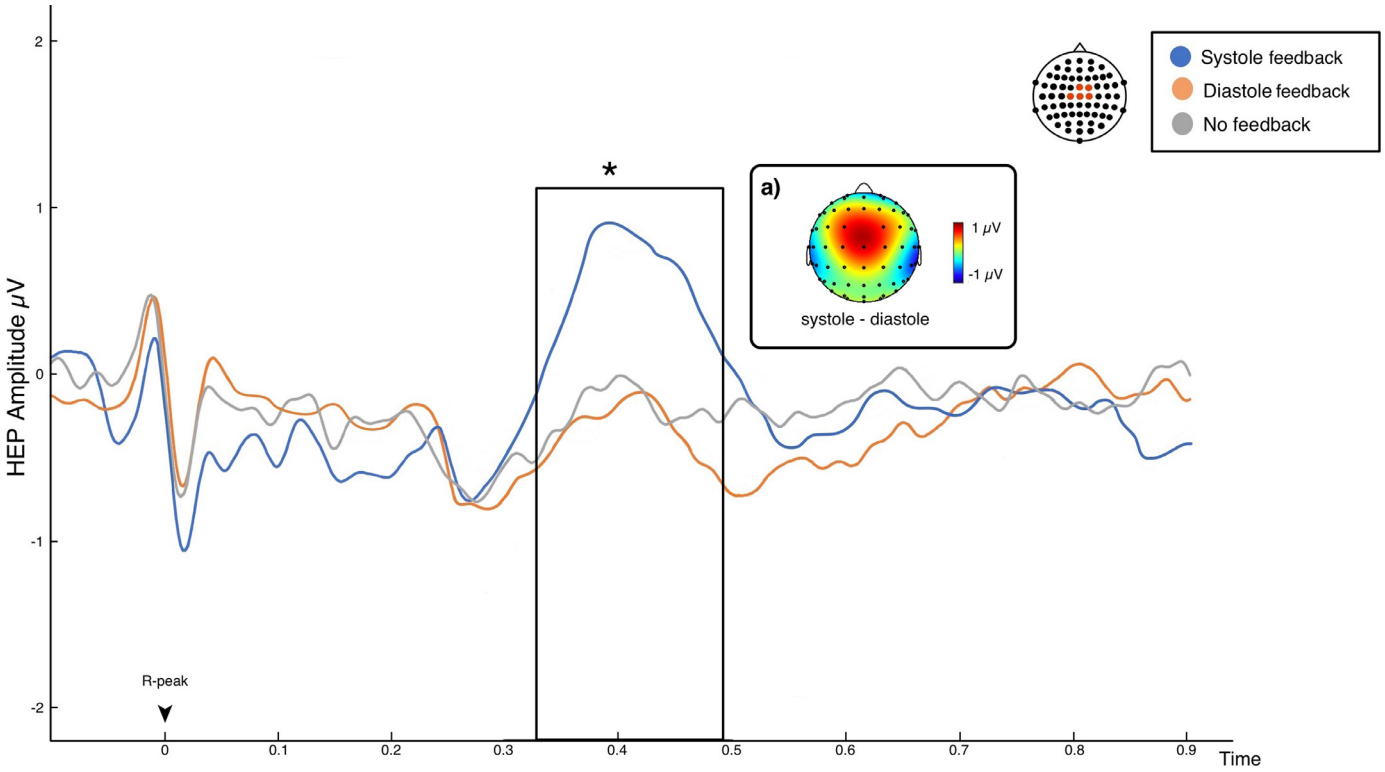

Fig. 3. HEP waveforms across the three biofeedback conditions. HEP expression was significantly higher for systole compared to diastole and no cardiac feedback. Uncorrected waveforms are shown in supplementary information (Fig. 2a) **a)** Topography shows the difference between diastole activation subtracted from systole activity.

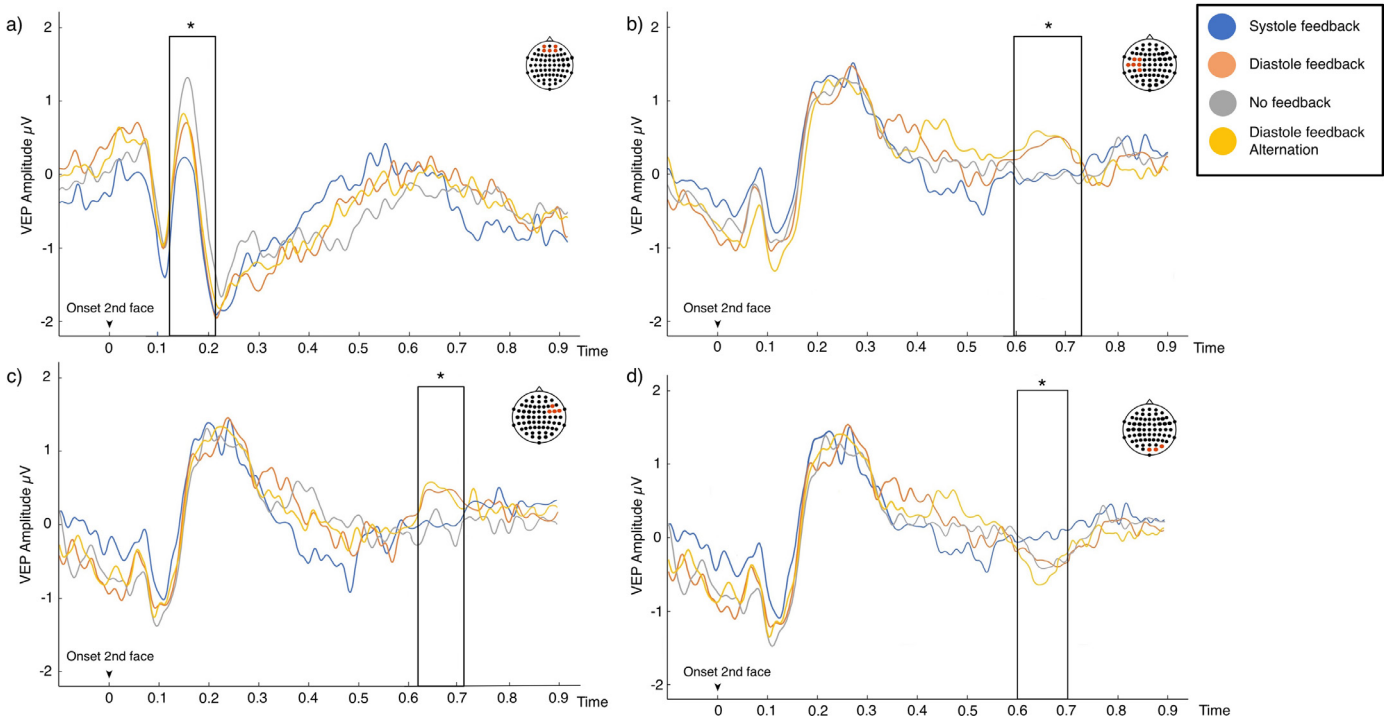

Fig. 4. VEP waveforms in response to viewing the second facial expression. **a)** We observed significantly reduced P2 amplitudes for repeated expressions following systole biofeedback compared to diastole and no biofeedback. **b)** P600 across left fronto-parietal, **c)** right-frontal and **d)** occipital electrodes sites. Amplitudes were significantly reduced for systolic relative to diastolic cardiac biofeedback. *Note:* Diastole feedback alternation (yellow waveforms) depicts activity in trials where the first neutral face was followed by an angry expression for the 2nd face presentation.

t = 8.237^{09}, p = .002) for a time window of 620 to 710 ms. Analysis of this region returned a main effect of feedback type [F(2,44] = 7.66, p = .002, η_P^2 = 0.26; BF = 28.55]. Once again, we found significantly reduced VEP amplitudes to the repeated face if it followed systolic (-0.11 μV) compared to diastolic (0.25 μV) biofeedback [t(22) = -3.9, p < .001, 95% CI [-0.72, -0.16], Cohen's d = 0.81; see Fig. 4c]. The third area of interest comprised right occipital electrode sites (Oz, O2, PO10; t = 2.135^{07}, p = .007) for a time window of 602 to 700 ms. Once again, we observed a main effect of feedback type [F(2,44) = 6.01, p = .008, η_P^2 = 0.21; BF = 9.34]. Simple main effects again revealed significantly reduced VEP amplitudes to the repeated face following systolic heartbeat feedback (0.12 μV) compared to both diastolic (-0.42 μV) feedback [t(22) = 3.21, p = .008, 95% CI [0.14, 1.13], Cohen's d = 0.67]and no (-0.46 μV) heartbeat biofeedback [t(22) = 2.75, p = .002, 95% CI [0.05, 1.04], Cohen's d = 0.57; see Fig. 4d].

3.4. HEP after the repeated face

The permutation test found no significant differences between systolic and diastolic feedback for any electrodes or time windows (all p_s > .05 after correction). Therefore, we did not conduct any further analysis for this HEP component.

3.5. Correct responses on control trials

Participants were able to score a total of 80 correct responses on control trials (20 per condition). Generally, performance was high across all trials (93.4 % hits) signifying that participants paid attention to the task. In addition, we observed a main effect of feedback type [F(2,46) = 27.45, p < .001, η_P^2 = 0.54, BF > 9.6^{7}] which showed that participants had fewer correct responses on control trials following diastolic feedback (84.5 % hits) compared to systolic feedback (97.5 % hits) [t(22) = 6.58, p < .001, 95% CI [1.6, 3.53], Cohen's d = 1.34] and no heartbeat feedback (96.5 % hits) [t(22) = -6.24, p < .001, 95% CI [-3.4, -1.47], Cohen's d = 1.27].

3.6. Control analysis

To test whether auditory biofeedback coincided with actual R- and T-wave activity and to investigate potential differences between both conditions, we calculated the average interval between the R-peak and T-wave and the onset of the tone. Results showed that for the diastole condition, tones were presented within 47.29 ms (∓ 23.60) of the R-peak while for the T-wave tones followed at an average interval of 49.77 ms (∓ 31.78). We ran a paired- samples t-test between both conditions and found no difference between the timings (p > .05). Findings thus highlight that our manipulation was equally successful in presenting biofeedback at a close interval to the actual cardiac event in both systole and diastole conditions.

To ensure HEP amplitudes reflected cortical heartbeat processing, we conducted two further control analysis. First, we created a second control distribution with surrogate R-peaks using the permutation analysis. Results showed that the previously found effect across the central electrode pool at 318 to 494 ms post R-peak retained significance relative to the surrogate R-peak control contribution (FCz, Cz, FC2, C1, C2; p = .0028). We can therefore conclude that HEP amplitudes used for the primary analysis reflect sequential cortical heartbeat processing in response to auditory feedback and are unrelated to other spurious cardiac and respiratory parameters. Secondly, we compared peak R-waves and mean T-wave activity across the three feedback conditions for the entire time window during which biofeedback was presented (~ 5000 ms). We found no differences in their expression between any of the feedback types for the entire time window [F(2,44) = 1.02, p = 3.84, BF = 0.0047]. We further compared ECG wave amplitude extracted for the 300 – 500 ms time window of biofeedback for which we report HEP effects. We found no differences in amplitude across any of the three feedback conditions [F(2,44) = 1.03, p = 3.99, BF = 0.0038]. We can thus conclude that HEP amplitude across the different biofeedback conditions manifested independently of potential differences in cardiac parameters.

We also considered whether increased autonomic arousal from diastolic heartbeat feedback may impact HEP and VEP amplitude, producing effects unrelated to the higher-order sensory processing we were investigating. To test for this, we included a fourth 'arousal' condition in which we followed diastolic feedback to the first face with a different second face showing an arousing angry expression. As a measure of homeostatic arousal, we first compared interbeat intervals and heartrate variability to the first neutral face between all three experimental conditions. We observed no significant differences in either measure (all p_s > .05, BF < .37). We proceeded to compare interbeat intervals and heartrate variability elicited by the first face in our experimental conditions with that elicited by the first face in our control condition in which participants anticipated diastolic feedback to be followed by an angry arousing face. This anticipation produced significant heartbeat deceleration in the control condition (M = 836 ms, SD = 68 ms) which significantly differed to interbeat intervals elicited by the neutral face in all three experimental conditions (M_pooled = 813 ms, SD = 107 ms, smallest p = 0.39; BF > 4.78). We observed no significant differences in heartbeat variability (all p_s > .05; BF < .83). Results hereby indicated that while diastolic feedback by itself did not induce arousal, pairing it with an angry facial expression was successful at eliciting homeostatic arousal (see Table 1). Finally, we correlated both cardiac measures with HEP amplitude to test whether changes of HEP activity were connected to fluctuations of these parameters. We observed no significant association between HEP amplitude and either interbeat intervals (r = .017, p = .21) or heartrate variability (r = .022, p = .19), indicating that the observed changes to the HEP are reflective of higher order cognitive operations rather than low level autonomic changes.

We then re-calculated our ANOVA for VEP amplitudes and correct behavioural responses including systolic vs. diastolic vs. none vs. diastolic alternation as the levels of FEEDBACK TYPE. The model for VEP amplitudes in the early time window found the same main effect of feedback type [F(3,66) = 7.22, p = .003, η_P^2 = 0.26, BF = 10.31]. Importantly, we found no significant difference between the original diastolic and the diastolic alternation condition (all p_s < .05). Similarly, the model for VEP amplitudes in the later time window showed the same main effect of feedback type for right frontal [F(3,66) = 5.38, p = .002, η_P^2 = 0.20, BF = 18.09], left parietal [F(3,66) = 6.41, p = .001, η_P^2 = 0.23; BF = 48.38] and left occipital regions [F(3,66) = 6.03, p = .004, η_P^2 = 0.22; BF = 31.6]. Again, we observed no significant difference between the original diastolic and the diastolic alternation condition (all p_s < .05). The model for correct responses likewise produced the main effect of feedback type [F(3,66) = 238.42, p < .001, η_P^2 = 0.91, BF > 25.7^{32}]. However, again we found no difference between correct responses on the original diastole and diastole alternation feedback trials (p > .05). This indicates that low level autonomic arousal is unlikely to be responsible for the effects reported in our primary analysis.

4. Discussion

Our body is both the generative source and instrument of our worldly experience. In line with this, past research has established that interoceptive processing can influence external perception (Garfinkel et al., 2014; Park et al., 2014; Marshall et al., 2019a) while external sensory information can alter the expression of interoceptive measures (Salomon et al., 2016; Sel et al., 2017; Marshall et al., 2018b; Hodossy and Tsakiris, 2020). In this study, we tested whether a manipulation of interoceptive heartbeat signals by means of auditory heartbeat feedback affected the sensory processing of internal and external information. We observed that the alignment of auditory heartbeat biofeedback with internal cardiac signalling enhanced amplitudes of the heartbeat evoked potential and reduced visual and auditory evoked poten-

Table 1
Means (SD) for autonomic cardiac parameters measured across experimental and control conditions.

	Experimental			Control
	Systole feedback	Diastole feedback	No feedback	Diastole feedback
Interbeat intervals (ms)	818 (101)	812 (122)	810 (98)	836 (112)*
Heartrate variability (ms)	33.76 (12.33)	31.82 (11.83)	33.84 (12.39)	32.94 (11.74)

Note.
* denotes significant differences between the control and all three experimental conditions (exp. systole vs. control: $t(22) = 2.35$, $p = .03$; exp. diastole vs. control: $t(22) = 3.21$, $p = .025$; exp. no vs. control: $t(22) = 2.95$, $p = .03$).

tials in response to repeating external stimuli. Our data hereby provides direct evidence that external cues are able to enhance interoceptive processing which in turn carries substantial benefits for exteroceptive sensory processing.

Higher HEP amplitudes have been linked to enhanced conscious awareness of one's own heartbeat (Pollatos and Schandry, 2004). In addition, a large body of work demonstrates that subconscious enhancement of the HEP as a result of contingent biofeedback (Canales-Johnson et al., 2015) or stimulus repetitions (Gentsch et al., 2019) coincide with improved perception and behaviour. Canales-Johnson and colleagues (2015) observed higher HEP amplitudes among participants who were able to use heartbeat biofeedback to tap more accurately to their heartbeat. Our own work demonstrates that HEP elevation after stimulus repetitions coincides with improved visual perception (Marshall et al., 2019a) and enhanced action planning and execution (Marshall et al., 2019b). Similarly, Sel and colleagues (2017) reported that a visual pulse sheet overlaid on the picture of a participant's face morphed with that of another led to higher HEP amplitudes and greater self-identification if pulses were delivered synchronously rather than asynchronously to participants' heartbeats. Results to this effect point to HEP elevation reflecting an enhancement of interoceptive cardiac processing which leads to conscious effects such as greater self-identification and heartbeat accuracy as well as subconscious improvements to perception and action. There is a general consensus within the growing field of interoceptive research that effects such as the previously discussed HEP modulations reflect a process of interoceptive predictive coding. HEP elevations are thus taken as the successful integration of accurate predictions with afferent information which has been achieved via experimental manipulations such as contingent cardiac biofeedback or by repeating stimuli that elicit similar autonomic responses. Specifically, our own work has shown that repeating affective facial expressions elicit highly similar patterns of cardiac responses which can lead to both enhancements or reductions of HEP amplitudes (Marshall et al., 2019b). This suggests that the brain's ability to form a representative prediction allows the dynamic allocation of resources for internal cardiac processing. Our current findings add important information to this emerging picture. In line with forgone work (Canales-Johnson et al., 2015; Sel et al., 2017; Marshall et al., 2017) synchronous cardiac feedback linked to the systole produced significant HEP enhancement relative to diastole-linked or no heartbeat feedback. This suggests that the alignment of exteroceptive with interoceptive signalling enabled an increased cognitive focus on the processing of the heartbeat signal and importantly, demonstrates that exteroceptive signals (i.e. our exteroceptive manipulation of the cardiac signal) aligned with predictively modelled heartbeat feedback to the brain can enhance interoceptive integration.

In our previous work (Marshall et al., 2017; Marshall et al., 2018b) our experimental manipulation presented no biofeedback but instead consisted of either repeating or alternating a neutral with an angry facial expression. In these experiments, we observed significant HEP modulation in the inter-trial interval following a repeat of the same facial expression. This suggests that the match between the affective cardiac response elicited by the first and second face modulated the subsequent HEP. Despite our repetition of neutral facial expressions, we did not reproduce this effect in our current study. One possible reason may be that HEP modulations resulting from experimental manipulations are transitory and rather short-lived in nature. The biofeedback manipulation in this study occurred much earlier (during presentation of the first face) than our manipulations in previous studies (during presentation of the second face). Results of the current study demonstrate that the effects of presenting cardiac feedback while participants viewed the first face had a lasting impact on exteroceptive processing of the second facial stimulus. However, potential differences elicited by systolic and diastolic biofeedback may not have lasted long enough to produce a second modulation of the later HEP component. A further difference to our previous work is that the initial face was presented for a long duration (> 4 s) in this experiment. This may have led to interoceptive adaptation processes whose nature differ from the effects reported in our foregone studies where the stimulus repetition sequence was much faster and effects may only have manifested by the time participants encountered the second face. Finally, it should be noted that our earlier findings relied on HEP comparisons across repeated and alternated trials for different types of emotional expressions. Neither of these conditions are present in the current study. A further possibility may therefore be that our biofeedback manipulation qualitatively differs from our earlier manipulations which involve the predictability of an upcoming stimulus and does not impact the HEP resulting from a repeating stimulus sequence.

The presentation of contingent cardiac feedback also produced an effect in the exteroceptive domain. We observed an auditory evoked potential whose morphology suggests an auditory P3 which manifested over right-frontal electrode sites. For this component, we observed a significant interaction between feedback type and tone representation which highlighted that for systolic heartbeat feedback, P3 activity successively decreased across the four auditory heartbeat representations. Importantly, we observed no such stepwise decrease for the diastolic feedback condition in which the same auditory stimulus was delivered. Repetition suppression effects are seen as one of the prime indicators of predictive processing in the field of exteroceptive perception (Desimone, 1996; Henson, 2003) and are taken to reflect the refinement of cognitive resources for a particular type of sensory input that the brain can accurately anticipate (Summerfield et al., 2011; Alink et al., 2010; Todorovic et al., 2011). The frontal P3 has been linked to voluntary attention switching (Escera et al., 2000; Debener et al., 2002) as well as in-depth stimulus evaluation based on memory and context updating (Kok, 2001; Polich, 2007). Importantly, work has shown that it decreases in response to stimuli that can be accurately predicted (Bennington and Polich 1999). Our approach of extracting P3 amplitude to each tone representation thus captured the stepwise refinement of resource allocation which was only present in the condition in which external cardiac feedback coincided with internal baroreceptor activity. Results hereby provide strong evidence that the alignment of external with interoceptive signals aids the predictive integration of external stimuli and enables the refinement of cognitive resources at a high level of stimulus processing.

In addition, we observed significant suppression of VEP amplitudes in response to the repeated face in the systole feedback condition. This effect manifested in an early P2 as well as a later P600 component. Sup-

pression of the P2 potential corresponds to our past work in which we contrasted HEP and early VEP amplitudes to repeated versus alternated iterations of facial expressions (Marshall et al., 2017; Gentsch et al., 2019; Marshall et al., 2018b). In these studies, we hypothesised that the highly similar cardiac patterns elicited by viewing the affective stimuli allowed an accurate match between the prior (adjusted after viewing the first face) and afferent sensory information elicited by the second face which enabled the observed changes to both types of cortical markers. In the current study, our aim was to produce a direct manipulation of the way the prior is processed by presenting contingent or misaligned biofeedback while participants viewed the first face. Our findings suggest the different biofeedback conditions had a significant impact on the predictive process: contingent feedback at systole produced a similar suppression effect reported in our previous studies while diastole feedback did not, even though affective stimuli were repeated in both conditions. In addition to early suppression effects, our current manipulation also produced effects for the later P600 component. This late positive potential has been linked to repetition effects (Kim et al., 2012) and is implicated in higher order processes such as memory recall (Voss et al., 2010) or the processing of complex auditory signals such as sentences (Weber and Indefrey, 2009). Direct cardiac feedback at systole thus created suppression effects highlighting more efficient visual processing in cortical markers of both low and higher order cognitive processes. Our results are hereby able to make more direct assumptions about the way in which enhanced integration of interoceptive signals carries benefits for exteroceptive perception at multiple hierarchical levels. Several studies report a link between interoceptive processing and external perception (Park et al., 2014; Salomon et al., 2016; Garfinkel et al., 2014). Salomon and colleagues (2016) suggest that the modulation of visual perception by cardiac signals may be the result of a homeostatic regulation process which monitors but also suppresses the widespread sensory impacts the heartbeat exerts on the body. Downregulation of the tactile, proprioceptive, auditory and visual side-effects produced by the heart contracting is, according to the authors, a prerequisite to ensure accurate perception of the external environment. Stimuli linked to certain phases of the heartbeat may thus suffer from the same downregulation process and become less salient. In line with this, increased HEP amplitudes do not always enhance external perception but have also been shown to correlated negatively with perceptual events linked to for example somatosensory experience (Al et al., 2020). Al and colleagues interpreted this negative relationship between somatosensory sensitivity and HEP amplitude as the result of attentional shifts between heartbeats and the external environment, which is reflected by the changes in HEP expression (Garcia-Cordero et al., 2017; Petzschner et al., 2019). Following this line of argument, the HEP elevation observed in this study might also reflect increased attention to heartbeats during systole feedback conditions. However, while this offers a plausible account of the way in which cardiac signals may influence exteroception, it does not account for findings which highlight that heartbeat-linked stimuli have a perceptual advantage. Garfinkel and Critchley (2016) suggest that cardiac fluctuations may act as a gating mechanism, dictating the strength of sensory sampling and the contents of perceptual consciousness. Similarly, Allen and colleagues Allen et al (2019) introduced a simulation model of exteroception coupled to interoceptive cardiac processing which suggests that visual sampling may be less precise or unavailable during certain phases of the cardiac cycle. However, rather than purely a perceptual advantage our findings suggest that enhanced interoceptive integration through contingent heartbeat feedback allowed the refinement of exteroceptive resources allocated to processing the visual stimulus. We therefore suggest that intero- and exteroception draw on a joint pool of cognitive resources which are allocated according to the principles of predictive coding. Successful processing in either domain frees up resources which can be invested to process other types of (intero- or exteroceptive) sensory information more successfully, potentially through the formation of more accurate and precise priors. Thus, a processing advantage in the interoceptive domain would carry over to exteroceptive processing and vice versa. Past work has shown that attentional resources are shared between intero- and exteroception. For example, Petzschner and colleagues (2019) have highlighted the trade-off between internal and external domains by demonstrating that amplitudes of the heartbeat evoked potential can be enhanced or reduced by drawing participants' attention to either the interoceptive or exteroceptive domain. Furthermore, studies have highlighted that effective interoceptive processing can have a facilitating effect on exteroceptive attentional performance. Matthias et al. (2009) demonstrated that participants with higher levels of interoceptive accuracy performed significantly above participants with low accuracy on tasks of selective and divided attention. Together, these findings could suggest that more successful interoceptive integration might aid noise cancellation of repeating exteroceptive information which may result in a decreased perception of weak sensory stimuli as well as an increased perception of salient exteroceptive information. Our findings support this account by highlighting a weak yet significant association between HEP and AEP activity, demonstrating that successful interoceptive integration (i.e. elevation of the HEP) coincided with efficient processing of the external heartbeat feedback (i.e. a reduction of the P3). Similarly, our behavioural results support this theory. Participants were significantly less likely to respond to control trials when they appeared on a face following diastolic heartbeat feedback. This suggests that the dichotomy between internal and external heartbeat signalling placed higher demands on interoceptive processing, making participants less likely to perceive and execute a timely response to the brief visual action cue.

Finally, we would like to highlight a potential limitation of our study as well as a topic of consideration for the field of research coupling stimuli to different phases of the cardiac cycle. In our study, we conceptualised the R-peak + 0 ms as the diastole and the R-peak + 290 ms as the systole condition. This choice was based on forgone work reporting promising findings with this choice of time window (Garfinkel et al., 2014; Salomon et al., 2016). However, the R-peak marks the point at which the ventricular diastole ends and the systole begins. Using this time point therefore gives rise to differing interpretations of what constitutes the systole and diastole phases across research groups (for example Adelhöfer et al., 2020 vs Garfinkel et al., 2014.). Other studies have conceptualised the diastole as the p-wave at -50/-100 ms pre R-peak (Rae et al., 2018) or as the interval following the T-wave at R-peak +400/+500 ms (Azevedo et al., 2016; Ambrosini et al., 2019) which may constitute a more clear-cut approach and avoid the potential confusion arising from choosing the R-peak itself as a diastole marker.

To conclude, our results are to the best of our knowledge the first to show a direct influence of interoceptive feedback on sensory predictions and capture the temporal and neural processes underlying this effect via EEG. We hereby extend the influential literature and theory of the predictive brain in humans. They further add to basic neuroscientific research on human cognition by highlighting the importance of internal bodily processes for successful external perception. The measures in this study capture implicit enhancements of internal and external signal processing. An important further step would be to explore whether they can be actively applied to improve interoceptive awareness and external perception and action. Given the beneficial biofeedback effects reported in this study as well as the established treatment benefits of biofeedback for common mental health issues, a further contribution would be to explore the duration of these effects with the goal of ascertaining whether the periodic delivery of biofeedback, for example via the use of a pulsometer or a fitness tracking watch, may carry durable advantages for mental health, internal bodily processing as well as perceptual interactions with the external environment.

Data and code availablilty

We hereby declare that our code and our data, as well as our materials are available from the authors of this study on reasonable request. In accord with the guidelines for good practive

advocated by the funding body of this research (Deutsch Forschungsgemeinschaft, DFG), all data and code are also publicly available via the Open Science Framework repository under the following link: https://osf.io/6waj9/?view_only=f9e25c0bbf2140c4a813eb41695dca1e.

Contributions

A.C.M., A.G.E. and S.S-B. designed the study. A.C.M. acquired and analysed the data. A.C.M., A.G.E. and S.S-B. wrote the paper.

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Data availability

Data and materials of this study are archived online at: https://osf.io/6waj9/?view_only=f9e25c0bbf2140c4a813eb41695dca1e.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119011.

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