The heartbeat-evoked potential in young and older adults during attention orienting

ABREVIATED TITLE Attention orienting and the neural responses to heartbeats

Francesca Aprile[1], Marco Simões[1,3], Jorge Henriques[3], Paulo Carvalho[3], Miguel Castelo-Branco[1,2], Alejandra Sel[4], Maria J. Ribeiro[1, 2, *]

1 - Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT), Institute for Nuclear Sciences Applied to Health (ICNAS), University of Coimbra, 3000-548 Coimbra, Portugal

2 - Faculty of Medicine, University of Coimbra, 3000-548 Coimbra, Portugal

3 – CISUC (Center for Informatics and Systems), University of Coimbra, Polo II, Pinhal de Marrocos, 3030-290 Coimbra, Portugal

4 - Centre for Brain Science, Department of Psychology, University of Essex, Wivenhoe Park, Colchester, CO4 3SQ, United Kingdom

* Corresponding author. Correspondence should be addressed to Maria Ribeiro at mjribeiro@fmed.uc.pt

Abstract

Cardiac cycle duration, or interbeat interval (IBI), is the period from one heartbeat to the next. IBI changes from cycle to cycle. Periods with longer IBI are associated with higher sensitivity to external sensory stimuli (more sensitive exteroception). Warning cues that precede target stimuli induce a state of attentive anticipation characterized by an increase in IBI (anticipatory cardiac deceleration) and faster reaction times. However, it is unclear which, if any, mechanism connects changes in IBI with reaction time. The heartbeat-evoked potential (HEP) is a cortical response evoked by the heartbeat which amplitude is modulated by attention locus and is associated with sensitivity to external sensory stimuli. HEP amplitude might be affected by IBI and mediate the association between cardiac output and cortical processing.

We investigated if the HEP was affected by warning cues as well as spontaneous fluctuations in IBI. We studied these phenomena in young and older people [N = 33 (26 women) and 29 (23 women); mean age 23 and 61 years], by analysing the electroencephalograms, electrocardiograms, and pupilograms simultaneously acquired during auditory cued simple reaction time and go/no-go tasks.

The warning cue did not induce significant changes in the HEP. Yet, fluctuations in IBI (not locked with the warning cue) affected the HEP, and HEP amplitude was associated with across participants reaction time differences in the older group. However, on a trial-by-trial basis, reaction time was independent from IBI fluctuations.

In conclusion, we found no evidence that HEP mediates the effect of attention orienting on reaction time.

Introduction

Cardiac cycle duration is the period between one heartbeat to the next, also known as the interbeat interval (IBI) as depicted in Figure 1A. IBI is inversely correlated with heart rate (when IBI increases, heart rate decreases). IBI changes from cycle-to-cycle largely due to the respiratory sinus arrhythmia but also due to changes in cognitive state. One example of the effect of cognitive state on the IBI is the effect of attention orienting in anticipation of an incoming sensory stimulus (Jennings and van der Molen, 2005). This state of attentive anticipation is associated with an increase in IBI, i.e., the heart starts beating slower, also known as anticipatory cardiac deceleration (Jennings et al., 1998; Gladwin et al., 2016; Ribeiro and Castelo-Branco, 2019a; Skora et al., 2022). Warning cues that predict incoming sensory stimuli evoke this state of attentive anticipation, characterized by simultaneous cardiac deceleration, pupil dilation, and frontal cortex activation (Jennings and van der Molen, 2005). Sensorimotor processing refers to all the neural processes that lead to sensory perception and terminate in a related motor response. Behaviourally, warning cues shorten reaction times through a mechanism that speeds up sensorimotor processing by altering late perception, response selection, and early motor processes (Hackley, 2009). Interestingly, across participants, the amplitude of the anticipatory cardiac deceleration correlates negatively with average reaction time suggesting a link between these two phenomena (Jennings et al., 1998; Reyes et al., 2015; Ribeiro and Castelo-Branco, 2019a).

Why does the heart slow down during attentive anticipation? Changes in IBI might contribute to the effect of warning cues on reaction time by, for example, increasing sensory sensitivity. In fact, spontaneous variations in IBI are associated with changes in the processing of external sensory stimuli. Besides changes in IBI that are evoked by task-relevant events like warning cues, IBI also changes due to factors independent of task performance, these are called ongoing or spontaneous fluctuations in IBI. When studying the effect of spontaneous fluctuations in IBI, Sandman et al. (1977) observed that periods of longer IBIs were associated with higher visual sensitivity (Sandman et al., 1977). However, the mechanism linking cardiac activity to sensorimotor processing is not fully clear.

The cardiac cycle can be divided in two phases, the systole, at the beginning of the cycle, and the diastole, at the end. At systole, the ventricles contract and blood is ejected into the aorta. At this point, the baroreceptors located in the vessels are activated in response to the pressure wave. In contrast, during the diastole, baroreceptor activity in minimal. Baroreceptor activity is transmitted to the brain where it attenuates cortical excitability hindering the processing of external stimuli (Skora et al., 2022). The slowdown of the heart during

attentive anticipation might serve to decrease the frequency of the baroreceptor signal thereby minimizing its impact on the processing of external stimuli.

Moreover, a separate but possibly related mechanism has been proposed that also links cardiac activity with the processing of external sensory stimuli. The heartbeat-evoked potential (HEP) is a neural response to heartbeats which can be measured non-invasively in humans using scalp electroencephalography (EEG) or magnetoencephalography (MEG) as the brain potential locked to the R or the T peak of the electrocardiogram (ECG). The amplitude of the HEP measured just before the onset of weak visual or somatosensory stimuli is associated with stimulus detection (Park et al., 2014; Al et al., 2020, 2021). The physiological origin of the HEP is thought to be multifaceted and to encompass baroreceptor activity, activity in cardiac neurons in the heart's wall, and the somatosensory sensation of the heartbeat in the skin (Park and Blanke, 2019). According to the idea that HEP amplitude is associated with the processing of incoming sensory stimuli, shifts in attention from internal bodily sensations to external sensations are associated with a decrease in HEP amplitude suggesting that weaker HEPs are associated with attention to external stimuli (Mai et al., 2018; Petzschner et al., 2019). As warning cues elicit an attention orienting response to external sensory stimuli, we hypothesize that warning cues besides evoking cardiac deceleration might also be associated with changes in HEP amplitude and that these two phenomena might even relate to changes in IBI associated with changes in HEP amplitude.

Aging affects heart rate and the preparatory cardiac deceleration. Older people have slower, less variable heart rate (Umetani et al., 1998), and weaker anticipatory cardiac deceleration responses (Jennings et al., 1990; Ribeiro and Castelo-Branco, 2019a). Interestingly, HEP amplitude measured during quiet rest is more positive in older people (Kamp et al., 2021). If, as it has been suggested, HEP amplitude reflects the activation of the baroreceptors and baroreceptors activity is associated with a decrease in cortical excitability, then this increase in HEP amplitude with aging might reflect a stronger effect of heartbeats on cortical excitability, and consequently reduced sensitivity to external sensations. Moreover, as heart rate fluctuations and anticipatory cardiac deceleration are reduced in older people, the hypothesized effect of the warning cue on the HEP might be attenuated in this population.

In this study, we investigated if anticipatory cardiac deceleration or spontaneous fluctuations in IBI are associated with changes in HEP amplitude in a way that might mediate the hypothesized effect of IBI on reaction time. As older people show reduced heart rate fluctuations and weaker cardiac deceleration responses, we included both young and older people in our study, hypothesizing that any impact of IBI on the HEP would be

weakened in older people. To explore these questions, we re-analysed a previously described dataset containing EEG, ECG and pupillography data from young and older adults, acquired during an auditory cued simple reaction time (RT) task and an auditory cued go/no-go task (Fig. 1A; Ribeiro and Castelo-Branco, 2021). In previous analyses of this dataset, we showed that while task accuracy was equivalent in both groups of participants, older people showed increased reaction time difference across tasks (Ribeiro and Castelo-Branco, 2019b). The warning cue evoked a cardiac deceleration response. We quantified the amplitude of this anticipatory cardiac deceleration response by measuring the amplitude of the IBI peak measured after the warning cue subtracted by the IBI just before the warning cue. Cardiac deceleration was stronger in the young group than in the older group and stronger in the go/no-go than the simple RT task (Ribeiro and Castelo-Branco, 2019a). Across-participants correlation analysis revealed that, in the young group, stronger cardiac deceleration correlated with faster reaction time suggesting an association with sensorimotor processing.

METHODS

Participants

Thirty-six young adults and thirty-nine older adults were included in this study. One young and four older participants presented a high number of ectopic beats in the ECG recordings and were excluded from the analyses. In addition, two young and six older participants presented ECG recordings with poor quality, difficult to segment. These were also excluded from analyses. We included 33 young adults (mean age ± SD = 23 ± 3 years; mean education ± SD = 16 ± 2 years; MoCA score = 27 ± 2; 26 women; 3 left-handed) and 29 older adults (mean age ± SD = 61 ± 5 years; mean education ± SD = 16 ± 4 years; MoCA score = 25 ± 3; 23 women; 1 left-handed). All participants had normal hearing and normal or corrected to normal vision; had no history of neurological, psychiatric, or vascular disease; and were not taking any psychotropic medications or beta-blockers. Five older participants were taking other types of medication to control blood pressure (angiotensin receptor blockers, angiotensin-converting enzyme inhibitors or calcium blockers). All participants were screened for dementia and scored above the cutoff in the Montreal Cognitive Assessment – MoCA (Freitas et al., 2011), and gave written informed consent (Ethics Committee of the Faculty of Medicine of the University of Coimbra, No. CE-002-2016).

Experimental design

Participants performed two auditory tasks; a cued simple reaction time task and a cued go/no-go task presented sequentially (Fig. 1B). The order of presentation was pseudorandomised and counterbalanced across participants. In the simple reaction time task, trials started with the presentation of an auditory cue (1500 Hz) followed by an auditory go stimulus (1700 Hz). In the go/no-go task, the trial started with the auditory cue (1500 Hz) followed by either the auditory go stimulus (1700 Hz, 80 trials) or an auditory no-go stimulus (1300 Hz, 20 trials) (Figure 1) (Ribeiro and Castelo-Branco, 2019a, 2019b). In each task, 17 % of the trials were cue-only trials, where only the auditory cue was pseudo-randomly presented (20 trials). The interval between the cue and the target and between the target and the onset of the next trial were drawn from a nonaging distribution, $-W*\ln(P)$, where W is the mean value of the interval distribution and P is a random number between 0 and 1 (Jennings et al., 1998). The cue-target interval was $1.5-0.25*\ln(P)$ in seconds, and the interval between the target and the next trial (cue) was $5.2-1*\ln(P)$ in seconds (median = 7.6 s, min= 6.7 s, max= 19.6 s). Under these conditions the median time interval between the cue and the target was 1.7 s (range: 1.5 - 4.1 s). The median time interval between the target and the cue of the subsequent trial was 5.9 s (range: 5.2 – 15.5 s).

Each task had 120 trials, with a short break halfway through the task. All auditory stimuli were suprathreshold and were presented for 250 ms. Participants were instructed to press a button with their right index finger as soon as the go stimulus was presented, and to withhold the response in the cue-only trials and in the go/no-go task when the no-go stimulus was presented. The tasks were presented with the Psychophysics Toolbox, version 3 (Brainard, 1997) in MATLAB (The MathWorks Company Ltd).

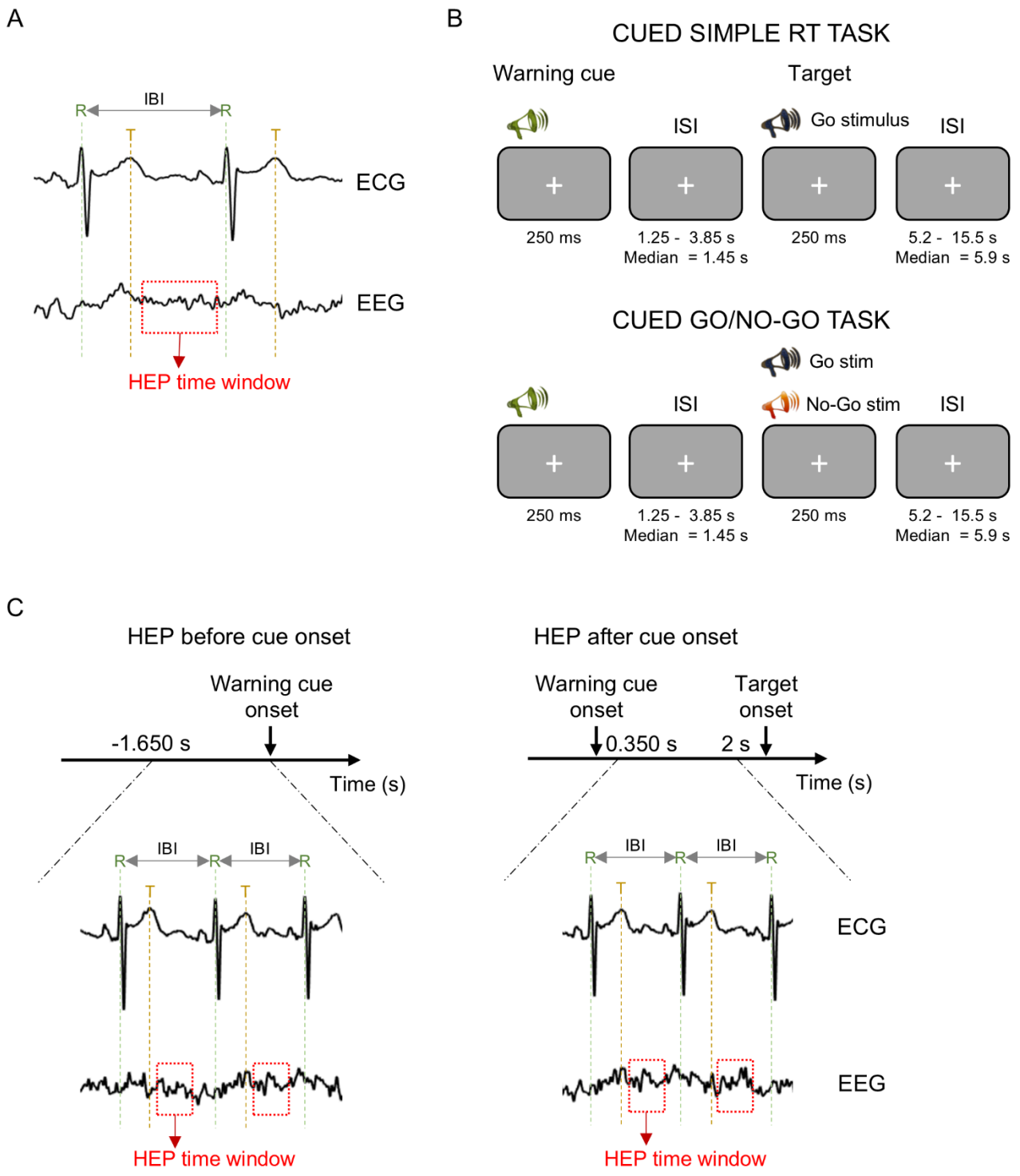

Figure 1. Behavioural task design and analyses procedures. **(A)** For each cardiac cycle, the interbeat interval (IBI) was calculated as the time interval between its R peak and the R peak of the subsequent cycle. The hearbeat-evoked potential (HEP) was analysed in a time window from 50 ms up to 350 ms after the T peak. The red box represents the HEP time window. **(B)** Participants performed two task conditions: a cued simple reaction time (RT) task and a cued go/no-go task. In both task conditions, the warning cue presented at the beginning of the trial was followed by target stimuli. In the simple RT task, the target stimuli was always a go stimulus, while in the go/no-go task the target stimulus could be a go stimulus (67

% of the trials) or a no-go stimulus (17 % of the trials). In both task conditions, 17 % of the trials were cue-only trials, where the target was not presented after the cue. Participants were instructed to respond with their right index finger as fast as possible upon detection of the go stimulus and to withhold the response in no-go trials and cue-only trials. **(C)** For the comparison of the HEP before and after the cue, the HEP was extracted in two time windows: before the cue from -1.65s up to cue onset and after the cue from .35 s up to 2 s after the cue.

ECG recording and analyses

The ECG data was recorded with bipolar electrodes attached to the participants' chest (500 Hz sampling rate) and downsampled offline to 250 Hz for further processing. The R and T peaks were identified using an in-house set of ECG analysis algorithms (Henriques et al., 2015), developed by the Adaptive Computation Group of CISUC, that offers a set of functionalities for the examination and interpretation of the ECG. The analysis process comprises a set of stages, including pre-processing and segmentation, data transformation, feature extraction, modeling, and validation. Particularly for the segmentation phase, a morphological transform approach was implemented (Sun et al., 2005), enabling the determination of the most important ECG fiducial points. These points enable the characterization of the main waves in the ECG, namely the QRS complex, the P and T waves, as well as the most relevant ECG intervals and segments.

The data was visually inspected to ensure correct peak detection and segmentation. In two participants, the in-house algorithm failed to detect the R and T peaks and instead these peaks were detected using the findpeaks.m function implemented in MATLAB.

EEG recording and analyses

The EEG signal was recorded using a 64-channel Neuroscan system (Compumedics EUROPE GmbH) with scalp electrodes placed according to the International 10–20 electrode system (500 Hz sampling rate). The reference was located between electrodes CPz and Cz and the ground between FPz and Fz. Eye movements and blinks were monitored using vertical and horizontal electrooculograms. Participants placed their heads in a forehead rest to allow for recording of pupillographic data (see Ribeiro and Castelo-Branco, 2019b) compromising the signal in channels FP1, FPz, and FP2, which were excluded from further analysis. Offline EEG analysis was performed with the EEGLAB (v2022.2, Delorme and Makeig, 2004) and MATLAB custom scripts. The data was digitally band-pass-filtered between 0.5-45 Hz and re-referenced to linked earlobes.

Physiological artefacts such as eye blinks, saccades and cardiac activity were corrected by means of independent component analysis. Cardiac independent components which time courses correlated significantly with the ECG signal were removed. In the individual datasets where no component correlated significantly with the ECG signal, then the component that presented the highest correlation coefficient was removed.

Heartbeat-evoked potentials (HEPs)

We focused our analyses on the HEP locked with the peak from the T wave as performed in previous studies (Park et al., 2014; Zhang et al., 2023). There were two reasons behind this choice. First, after the T wave of the ECG, during the heart relaxation period, the cardiac field artefact is minimum allowing for a better characterization of the neural response. Second, the QT interval of the ECG increases with ageing (Rabkin et al., 2016; Satpathy et al., 2017) and therefore, in the HEPs locked with the R peak, the T wave occurs at different times in the different age groups resulting in differences in the timing of the artefact associated with the T wave. Locking our analyses to the T peak allowed us to look at the HEPs of both groups independent of differences in the cardiac field artefact. For these reasons, we focused our statistical comparisons on the time window between 51 and 349 ms after the T peak (the heart relaxation period) where the cardiac field artefact is minimal (Park et al., 2014; Park and Blanke, 2019; Zhang et al., 2023). We confirmed in our dataset that the interval between the R and T peaks was indeed significantly longer in the older group (mean ± SD: young = 268 ± 26 ms; older = 284 ± 18 ms; independent samples *t*-test: $t_{(60)} = -2.85$, $p = .006$).

To compute the HEP, we segmented the data in 0.8 s segments, starting -0.2 s before the onset of the T peaks without baseline correction (number of epochs are detailed in Table 1). We chose to calculate the HEP without baseline correction because, given the cyclical nature of the HEP, any baseline period would contain activity from the previous HEP affecting its amplitude (Azzalini et al., 2019; Park and Blanke, 2019).

To ensure that the HEP calculated represent neural activity truly locked to the participants' heartbeat, we created surrogate T peaks by adding a random number between 0 and 1 to each peak latency value (Babo-Rebelo et al., 2016).

Table 1. Across-participants' mean ± standard deviation of number of cardiac cycles used in each of the analyses presented and number of trials included in the analyses of the effect of the warning cue.

	Young group (N = 33)		Older group (N = 29)	
	Simple RT	Go/no-go	Simple RT	Go/no-go
Number of cardiac cycles				
HEP and HEP vs IBI	1104 ± 148	1093 ± 153	998 ± 128	1008 ± 117
HEP vs IBI only long IBIs	879 ± 260	841 ± 327	992 ± 119	954 ± 162
Before the cue	136 ± 19	133 ± 19	123 ± 17	124 ± 16
After the cue	107 ± 16	103 ± 15	94 ± 15	96 ± 12
Number of trials				
Before the cue	117 ± 4	116 ± 5	116 ± 7	116 ± 5
After the cue	118 ± 3	116 ± 6	117 ± 5	116 ± 5

To investigate the effect of the warning cue on the HEP, we compared the HEP before cue onset (calculated in the time window from -1.65 s up to cue onset) with the HEP after cue onset (from .350 s up to 2 s after cue onset). These intervals were chosen to be large enough to maximize the number of cardiac cycles included while avoiding overlapping with the evoked potential induced by the cue and target stimuli. As the cue-target interval was variable and the minimum interval was 1.5 s, in the calculation of the HEP after the cue, there were some instances where the target was included in the HEP epoch. In these cases, the HEP epoch including the target was discarded. Note that we considered all the trials, including the rare trials (17 %) where the target was omitted (cue-only trials). As we studied only the period immediately after the warning cue during which participants could not know that the target was not going to be presented, these trials will be processed as the cue-target trials. Similarly, and for the same reason, in the go/no-go task, we included all trials in the analysis: go trials, no-go trials and cue-only trials. We were interested in the effect of the warning cue, before target onset, and this should be the same for all types of trials. Number of trials and cardiac cycles included in the analyses are detailed in Table 1.

For this analysis, it was necessary to correct for the baseline drift associated with the preparatory potential evoked by the cue, the Contingent Negative Variation (Azzalini et al., 2019; Ribeiro and Castelo-Branco, 2019b). With this aim, we calculated the surrogate HEPs in a time window before cue onset (-1.65 s before cue onset) and a time window after cue onset (from .350 s up to 2 s after cue onset, an interval that avoided the cue and

target evoked potentials). Then, we subtracted the trial-averaged surrogate HEP from the corresponding HEPs calculated in the same time window before or after cue-onset. To avoid adding noise to the HEP during the subtraction process, we first smoothed the trial averaged surrogate HEPs by filtering the data with a Gaussian window using the MATLAB function smoothdata.m with a moving window length of 150 points.

Calculation of interbeat interval (IBI) and average heart rate

For each cardiac cycle, IBI was calculated as the time interval between two consecutive R peaks in the ECG. For the comparison of IBI before and after cue onset, IBI was calculated within the same windows where HEP was calculated: before cue onset = -1.65 up to cue onset; after cue onset = 0.350 s to 2 s after cue onset. For the study of the effect of IBI ongoing fluctuations on HEP amplitude, we calculated the IBI for each cardiac cycle and within the same cycle extracted the T locked epoch where we calculated the HEP, as shown in Figure 1B.

Ectopic beats can lead to shorter or longer cardiac cycles and are more frequent in older adults (Mannina et al., 2021). We excluded from analyses all cardiac cycles associated with ectopic beats by excluding, within each participant and task condition, cycles with absolute IBI z-score higher than 4. Visual inspection of the data confirmed that this cut-off was appropriate to exclude all the ectopic beats.

Heart rate was calculated in beats per minute by dividing 60 by the IBI value in seconds.

General linear modelling of EEG data

Statistical analyses were performed by analysing all time points and all EEG channels using a hierarchical linear model approach, as implemented in the LIMO EEG toolbox, an open-source MATLAB toolbox (Pernet et al., 2011). Second level analysis (group level) were run using robust trimmed means methods. Results are reported corrected for multiple testing using spatial-temporal clustering with a cluster forming threshold of p = 0.05 (Pernet et al., 2015).

To study the effect of task condition and group on the HEP amplitude, we run a first level analysis (subjects level), by setting up a general linear model with two categorical regressors corresponding to the two task conditions, and processing all subjects single trials automatically (Bellec et al., 2012). In these first level analyses, all trials for each time point and channel were modelled as the sum of a constant term and the

coefficients for the two experimental conditions (simple RT and go/no-go). Parameter estimates were obtained using Ordinary Least Squares. At the second level analysis (group level), we run two analyses. First, we run a one-sample *t*-test on the trial averaged HEP amplitude to reveal where and when the HEP amplitude was significantly different from zero across all participants. Second, we run a robust repeated measures ANOVA testing the effect of task (within-subject factor) and the effect of group (between-subjects factor).

To compare the HEP amplitude before and after the cue, we modelled the data using only the second level analysis and the trial averaged HEP. This was because the correction for the baseline drift was done on the trial averaged HEP and therefore, we did not have single trial values to model at the first level. At the second level, we run a robust repeated measures ANOVA testing the effect of time (before *versus* after cue onset – within subject factor), the effect of task (simple RT *versus* go/no-go - within-subject factor) and the effect of group (between-subjects factor) on the HEP amplitude values.

To study the effect of IBI on the HEP amplitude, at the first level, a general linear model was set up with two categorical regressors corresponding to the two task conditions (isolating the effect of task) and two continuous regressors, one with the z-scored IBIs for the simple RT task and zeros in the go/no-go trials and the other with the go/no-go z-scored IBIs and zeros for the simple RT trials (Rousselet, 2011). With this design, we were able to compare the effect of IBI on HEP amplitude across tasks. Parameter estimates were obtained using Ordinary Least Squares. At the second level (group level), we run two analyses. First, we run a one-sample *t*-test on the coefficients for the continuous IBI predictors from the first level analysis. This revealed where and when the effect of IBI on HEP amplitude was significantly different from zero for the simple RT and go/no-go task conditions. Second, we run a robust repeated measures ANOVA testing the effect of task (within-subject factor) and the effect of group (between-subjects factor) on the coefficients from the IBI predictors. Similar analyses were run testing the effect of IBI on the amplitude of the ECG measured with our bipolar derivation.

Software for statistical analyses

Repeated measures ANOVAs for heart rate and IBI were run using IBM SPSS Statistics software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). Calculation for the test of the difference between two independent correlation coefficients was performed using the online calculator available from https://www.quantpsy.org/corrtest/corrtest.htm (Preacher, 2002). Other analyses were run in MATLAB (The MathWorks Company Ltd).

Results

HEP does not differ across age groups or task conditions

The HEP showed a significant positive potential in a cluster encompassing central, parietal, and occipital channels (Fig. 2). One-sample *t*-test analysis across all time points and EEG channels revealed that the HEP was significantly different from zero in one spatiotemporal cluster starting at 51 ms and ending at 349 ms after the T peak, with average amplitude of 0.201 ± 0.528 μV (mean ± across participants standard deviation; cluster *p* value = .002; Fig. 2A). Scalp topographies of the HEP revealed a midcentral positive potential in both groups of participants (Fig. 2B). Repeated measures ANOVA revealed no significant group or task effect or group x task interaction (Fig. 2C and D). Notably, randomizing the timing of the ECG events and recalculating the HEP resulted in an ERP (surrogate HEP) that was not significantly different from the baseline in any spatiotemporal cluster (Fig. 2E). Visual inspection of the ECG signal locked to the R peak confirms T peak delay (Fig. 2F), while in the ECG locked to the T peak, we can observe that the T peak in older people is slightly stronger and longer lasting (Fig. 2F). However, these differences were not statistically significant in our ECG derivation, after controlling for multiple comparisons.

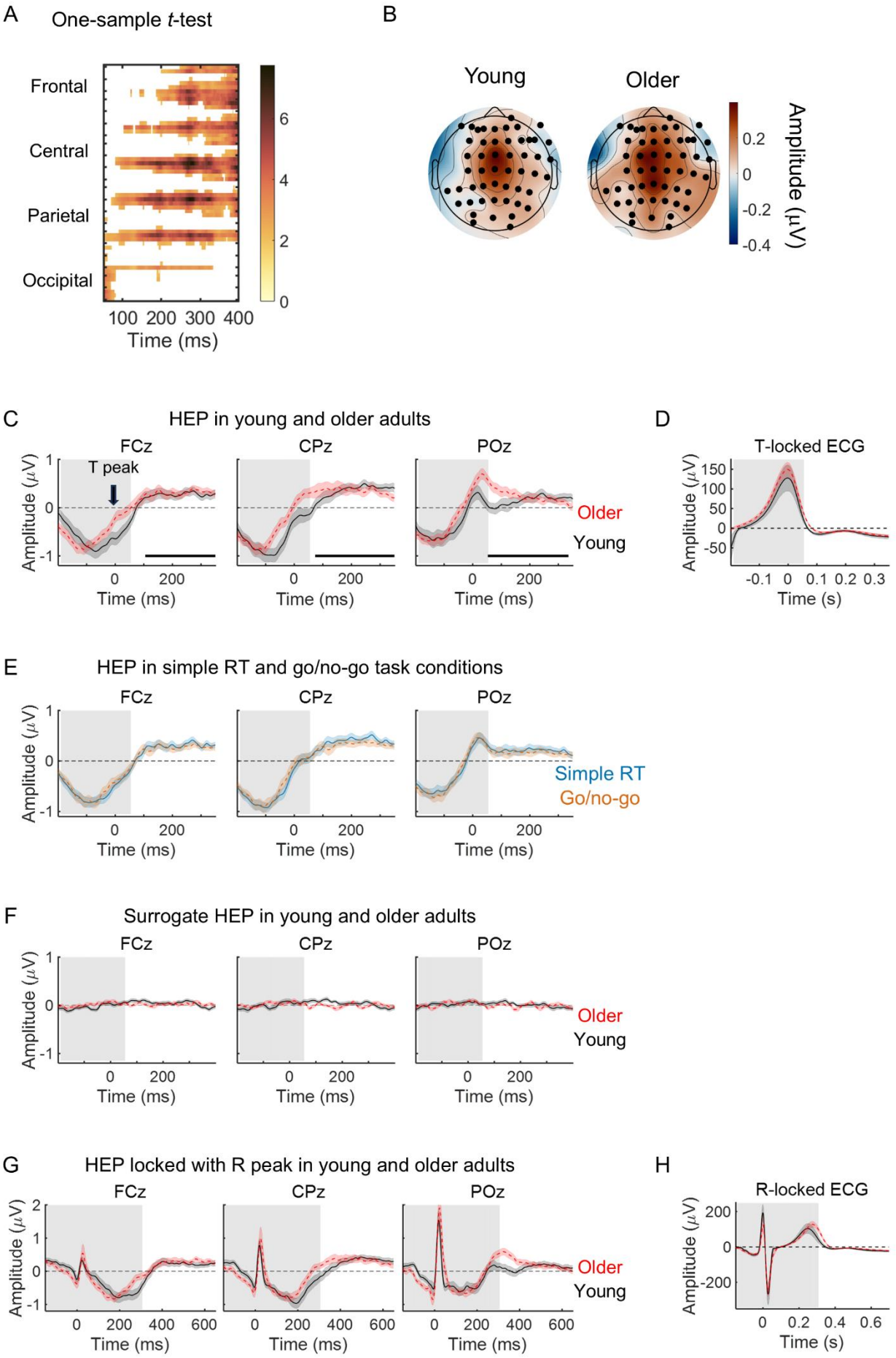
A
One-sample t-test
Frontal
Central
Parietal
Occipital
100 200 300 400
Time (ms)
6
4
2
0
B
Young
Older
0.2
0
-0.2
-0.4
Amplitude (μV)
C
HEP in young and older adults
FCz
CPz
POz
T peak
Amplitude (μV)
Time (ms)
Older
Young
D
T-locked ECG
Amplitude (μV)
Time (s)
E
HEP in simple RT and go/no-go task conditions
FCz
CPz
POz
Amplitude (μV)
Time (ms)
Simple RT
Go/no-go
F
Surrogate HEP in young and older adults
FCz
CPz
POz
Amplitude (μV)
Time (ms)
Older
Young
G
HEP locked with R peak in young and older adults
FCz
CPz
POz
Amplitude (μV)
Time (ms)
Older
Young
H
R-locked ECG
Amplitude (μV)
Time (s)

Figure 2. The HEP presented a positive potential with a midcentral topography that was not significantly different across age groups or task conditions. **(A)** One-sample *t*-test *t*-values within the spatiotemporal cluster where the amplitude of HEP was significantly different from zero, including all participants. **(B)** Scalp topographies of the grand average HEPs averaged within the time window 51-399 ms after the T peak. Black circles highlight the channels that belong to the significant spatiotemporal cluster where the HEP is significantly different from zero. **(C)** HEP in three midline channels measured in the young (black continuous line) and the older (red dashed line) groups. Horizontal black lines mark the time windows where the HEP is significantly different from zero. **(D)** ECG locked with the T peak measured in the young (black continuous line) and older (red dashed line) participants. **(E)** HEP in three midline channels measured during the simple RT (blue continuous line) and the go/no-go (orange dashed line) task conditions, averaged across all participants. **(F)** Surrogate HEP (locked to randomized ECG events) in three midline channels for the young (black continuous line) and the older (red dashed line) groups. **(G)** HEP locked with the R peak in three midline channels measured in the young (black continuous line) and the older (red dashed line) groups. **(H)** ECG locked with the T peak measured in the young (black continuous line) and older (red dashed line) participants. **(C-H)** The graphs plot the mean across participants ± standard error of the mean. Grey background highlights the time window not included in the statistical analyses.

HEP amplitude at the end of the cardiac cycle is associated with reaction time in older people

To determine if HEP amplitude is associated with the speed of sensorimotor processing, we investigated the association between average HEP amplitude and average reaction time (averaged across task conditions) across participants using regression analyses separately for each age group. We found that reaction time was significantly associated with HEP amplitude in the older group in one spatiotemporal cluster located at the end of the cardiac cycle (starting at 295 ms and ending at 349 ms after the T peak, p = .001; Fig. 3A) and encompassing left. frontal, central and parietal channels (Fig. 3B). No significant clusters were observed in the young group. To assert that the association between HEP amplitude and reaction time was significantly different across groups, we calculated the correlation coefficient between the HEP amplitude, averaged within the significant spatiotemporal cluster observed in the older group, and reaction time, in both groups of participants. Figure 3C represents the scatter plots of these two variables. Direct comparison of the resulting correlation coefficients using a Z-test revealed a significant difference across groups (p = .007) (Preacher, 2002). In the older group, HEP amplitude was more positive in the participants responding with slower reaction times compared with the participants presenting faster reaction times (Fig. 3C and D).

One source of interindividual differences in HEP amplitude might be differences in average heart rate. In fact, average heart rate and heart rate variability differ across age groups (Table 2). To investigate a possible link, we tested the association between average HEP amplitude and average heart rate. We found that HEP spatiotemporal dynamics was associated with average heart rate in the older group but not in the young group (Fig. 3C). In the older group, this association was significant in two small spatiotemporal clusters encompassing frontal channels (cluster 1 starting at 219 ms and ending at 235 ms after the T peak, p = .024; cluster 2 starting at 273 ms and ending at 287 ms after the T peak, p = .040; Fig. 3E and F). Older participants with faster heart rate showed higher HEP (Fig. 3G and H). Similarly to above, we calculated the correlation coefficients between the HEP amplitude, averaged within the significant spatiotemporal clusters observed in the older group, and heart rate, in both groups of participants. Figure 3C represents the scatter plots of these two variables. Direct comparison of the resulting correlation coefficients using a Z-test revealed that the correlation coefficients were not significantly different across groups (p = .067) (Preacher, 2002).

Table 2. Heart rate parameters, pupil-linked arousal measures, and power of alpha oscillations across task conditions and group

Mean ± standard deviation

	Young		Older	
	Simple RT	Go/no-go	Simple RT	Go/no-go
Heart rate average (bpm)	71 ± 10	71 ± 11	64 ± 7.8	65 ± 7.7
Heart rate standard deviation (bpm)	4.5 ± 1.4	4.6 ± 1.6	2.6 ± .9	2.7 ± .8
Heart rate range (bpm)	28 ± 9.4	29 ± 9.4	17 ± 5.8	17 ± 4.9

Repeated measures ANOVA

	Effect of task	Effect of group	Task x group interaction
Heart rate average	$F_{(1, 63)}$ = 1.88; p = .175	**$F_{(1, 63)}$ = 7.45; p = .008**	$F_{(1, 63)}$ = .860; p = .357
Heart rate standard deviation	$F_{(1, 63)}$ = .465; p = .498	**$F_{(1, 63)}$ = 42.9; p < .001**	$F_{(1, 63)}$ = .162; p = .689
Heart rate range	$F_{(1, 63)}$ = .632; p = .430	**$F_{(1, 63)}$ = 43.9; p < .001**	$F_{(1, 63)}$ = .373; p = .544

Notably, heart rate did not correlate with reaction time in either group of participants (young: r = .048, p = .791; older: r = .128, p = .508), suggesting that across participants heart rate differences do not explain the association between HEP and reaction time observed in the older group.

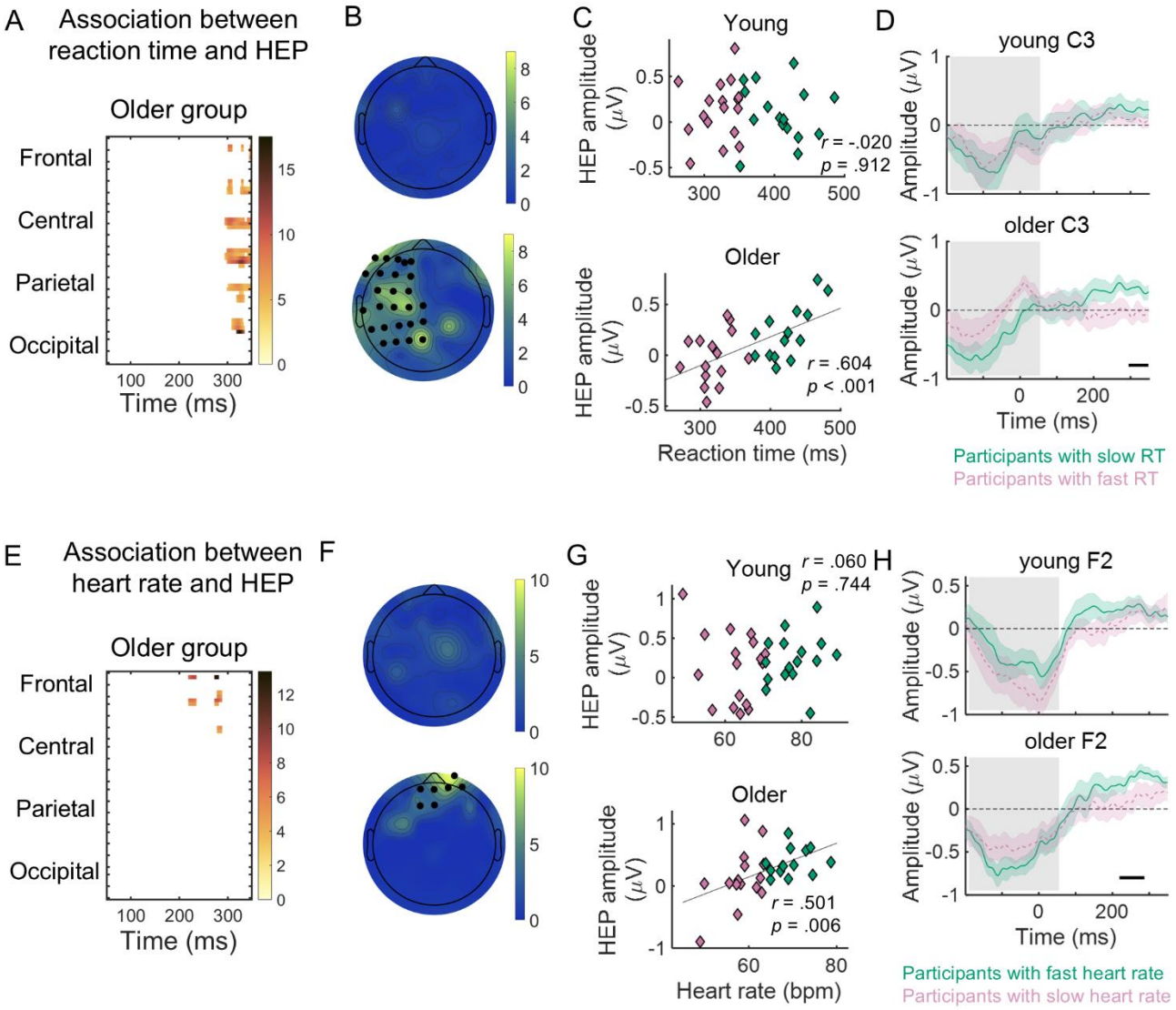

Figure 3. HEP shows significant associations with average reaction time and average heart rate. **(A)** Regression model *F*-values within the spatiotemporal cluster where the amplitude of HEP was significantly associated with average reaction time, in the older group. **(B)** Scalp topographies of the *F*-values from the regression model averaged within the time window from 250 to 350 ms after T peak. Black circles highlight the channels that belong to the significant spatiotemporal cluster where the regression model was significant. **(C)** Scatter plots of HEP amplitude averaged within the significant spatiotemporal clusters as a function of reaction time for the young (top) and the older (bottom) groups. Green and magenta data points represent participants that responded faster and slower (median split within each group), respectively. **(D)** HEP in the C3 channel measured in the young (top row) and the older (bottom row) groups. The horizontal black line shows the time window where the HEP was significantly associated with reaction time in the older group. Green continuous line represents data from participants that responded with slow reaction times and pink dashed line from participants that responded fast reaction times (median split within each group; same convention as in (C)). **(E)** Regression model *F*-values within the spatiotemporal clusters where the amplitude of HEP was significantly associated with average heart rate, in the young group (top) and in the older group (bottom). **(F)** Scalp topographies of the *F*-values from the regression model averaged within the

time window from 250 to 350 ms after T peak. Black circles highlight the channels that belong to the significant spatiotemporal cluster where the regression model was significant. **(G)** Scatter plots of HEP amplitude averaged within the significant spatiotemporal clusters as a function of average heart rate for the young (top) and the older (bottom) groups. Green and magenta data points represent participants with lower and higher hear rate (median split within each group), respectively. **(D)** HEP in EEG channel F2 measured in the young (top row) and the older (bottom row) groups. The horizontal black line shows the time windows where the HEP was significantly associated with heart rate. Green continuous line represents data from participants that present fast heart rates and the pink dashed line from participants that present slow heart rates (median split within each group; same as in (G)). **(D** and **H)** The graphs plot the mean across participants ± standard error of the mean.

Attentive anticipation is not associated with HEP changes

Next, we investigated if attention orienting induced by the warning cue was associated with changes in the HEP. We measured the HEP after cue onset, in a time window from .35 up to 2 s after the cue, and the HEP before the cue, in a time window with equal duration (1.65 s) placed just before cue onset (from -1.65 s up to cue onset). IBI measured in these time windows was significantly longer after the cue than before the cue [mean ± standard deviation (SD): young simple RT before cue 873 ± 125, after cue 882 ± 127; young go/no-go before cue 871 ± 133 after cue 878 ± 131; older simple RT before cue 957 ± 114, after cue 963 ± 110; older go/no-go before cue 940 ± 110, after cue 944 ± 109]. Repeated measures ANOVA of IBI with within-subject factors time (before cue onset *versus* after cue onset) and task (simple RT *versus* go/no-go), and between-subjects factor group (young *versus* older group) showed a main effect of time [$F_{(1, 60)} = 34.8$, $p < .001$] that did not differ between tasks [task x time interaction: $F_{(1, 60)} = 1.15$, $p = .289$] or participant groups [group x time interaction: $F_{(1, 60)} = 1.88$, $p = .176$] reflecting an overall cardiac deceleration after cue presentation. In addition, there was a main effect of group reflecting the fact that IBI was longer in the older versus the young participants [$F_{(1, 60)} = 6.15$, $p = .016$] and an overall effect of task [$F_{(1, 60)} = 4.38$, $p = .041$] with the go/no-go task associated with slightly shorter IBIs.

We then examined if this anticipatory state induced by the warning cue led to changes in HEP amplitude. To compare HEP amplitude before and after the cue onset, it was necessary to correct the baseline drift observed in the EEG signal after the cue due to the slow negative preparatory potential, the contingent negative variation (CNV) (Azzalini et al., 2019; Ribeiro and Castelo-Branco, 2019b). To this aim, we first computed the HEP in the time windows of interest (Fig. 4A). It was noticeable that the HEP after the cue appeared on top of a slowly

decreasing baseline. To correct for this drift, we calculated the surrogate HEP obtained before and after the cue by randomizing the T events and therefore breaking the link between the EEG and the ECG (see Methods). Visual inspection of the surrogate HEPs calculated before and after the cue revealed that after the cue there was a slowly evolving negative potential (a baseline drift) not locked to the ECG (Fig. 4B). We used this surrogate HEP to calculate the baseline drift evoked by the cue and subtracted it from the HEP to obtain the baseline drift corrected HEP containing only the activity locked to the T peak. To avoid adding noise to the HEP, we first smoothed the surrogate HEP before subtracting it (Fig. 4C). The baseline drift corrected HEPs before and after the cue were not significantly different (Fig. 4D). Repeated measures ANOVA across all time points and EEG channels did not reveal any spatiotemporal cluster presenting a significant effect of time (before *versus* after the cue), suggesting that, under our task conditions, the cardiac deceleration evoked by the cue did not result in significant changes in the HEP.

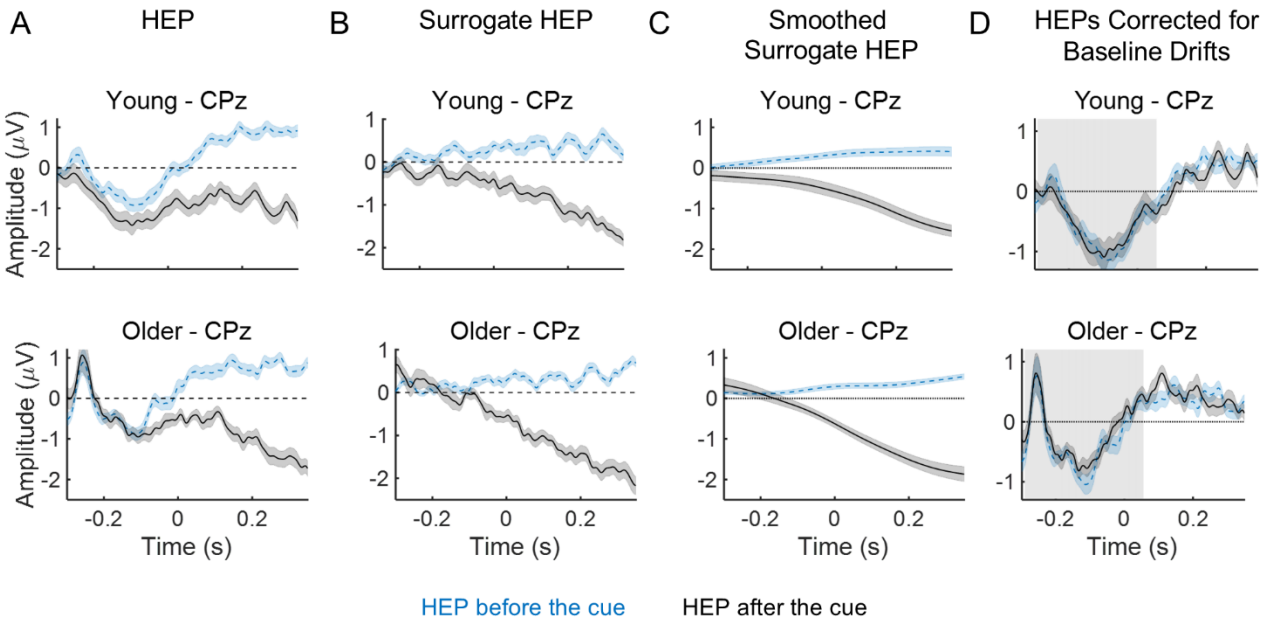

Figure 4. Heartbeat-evoked potential (HEP) measured after the cue is not significantly different from the HEP measured before the cue. **(A)** HEP before and after cue onset **(B)** Surrogate HEP before and after cue onset. **(C)** Smoothed surrogate HEP before and after cue onset. **(D)** HEP before and after cue onset corrected for baseline drift by subtracting the HEP from the smoothed surrogate HEP for each participant. Grey background highlights the time window not included in the statistical analyses. **(A-D)** HEP measured at channel CPz in the young and older groups. The graphs plot the mean across within group participants ± standard error of the mean. HEP after the cue plotted in black continuous line. HEP before the cue plotted in blue dashed line.

Within-subject HEP amplitude fluctuations with IBI differ across age groups

Absolute IBI, as opposed to preparatory cardiac deceleration, has also been associated with the efficiency of sensorimotor processing (Sandman et al., 1977). Ongoing fluctuations in cardiac cycle duration (IBI) might also be associated with fluctuations in the neural responses to heartbeats. Under our task conditions, the amplitude of the change in IBI associated with the anticipatory cardiac deceleration was small compared to the ongoing fluctuations in IBI observed throughout the task that are several orders of magnitude larger (mean ± SD IBI change evoked by the warning cue = 7 ± 9 ms; mean ± SD range of IBI fluctuations throughout the recordings = 294 ± 101 ms). Thus, it is possible that we did not observe any effect of the anticipatory cardiac deceleration on the HEP because this effect was small in comparison with the larger spontaneous IBI fluctuations. We investigated the effect of IBI fluctuations on the HEP using within-subject regression analyses including IBI as a predictor and HEP as response variable. One-sample *t*-test analyses revealed that the regression coefficients were significantly different from zero in a cluster encompassing most EEG channels in a time window from 51 ms up to 175 ms after the T peak in the simple RT task condition (p = .001) and in a time window from 51 ms up to 183 ms after the T peak in the go/no-go task condition (p = .001; Fig. 5A). In both task conditions, HEP amplitude was found to be more negative in longer cardiac cycles than in shorter cycles starting before the T peak up to around 200 ms after the T peak (Fig. 5A, C and D). Repeated measures ANOVA with within-subject factor task (simple RT *versus* go/no-go task) and group as between-subject factor (young *versus* older group), performed on the regression coefficients from the IBI predictors, revealed a significant group effect in a frontocentral cluster that starts at 183 ms and ends at 349 ms (p = .003), reflecting the fact that in frontal channels the regression coefficients were more negative in the young group (Fig. 5D). We found no significant effect of task condition or group x task interaction.

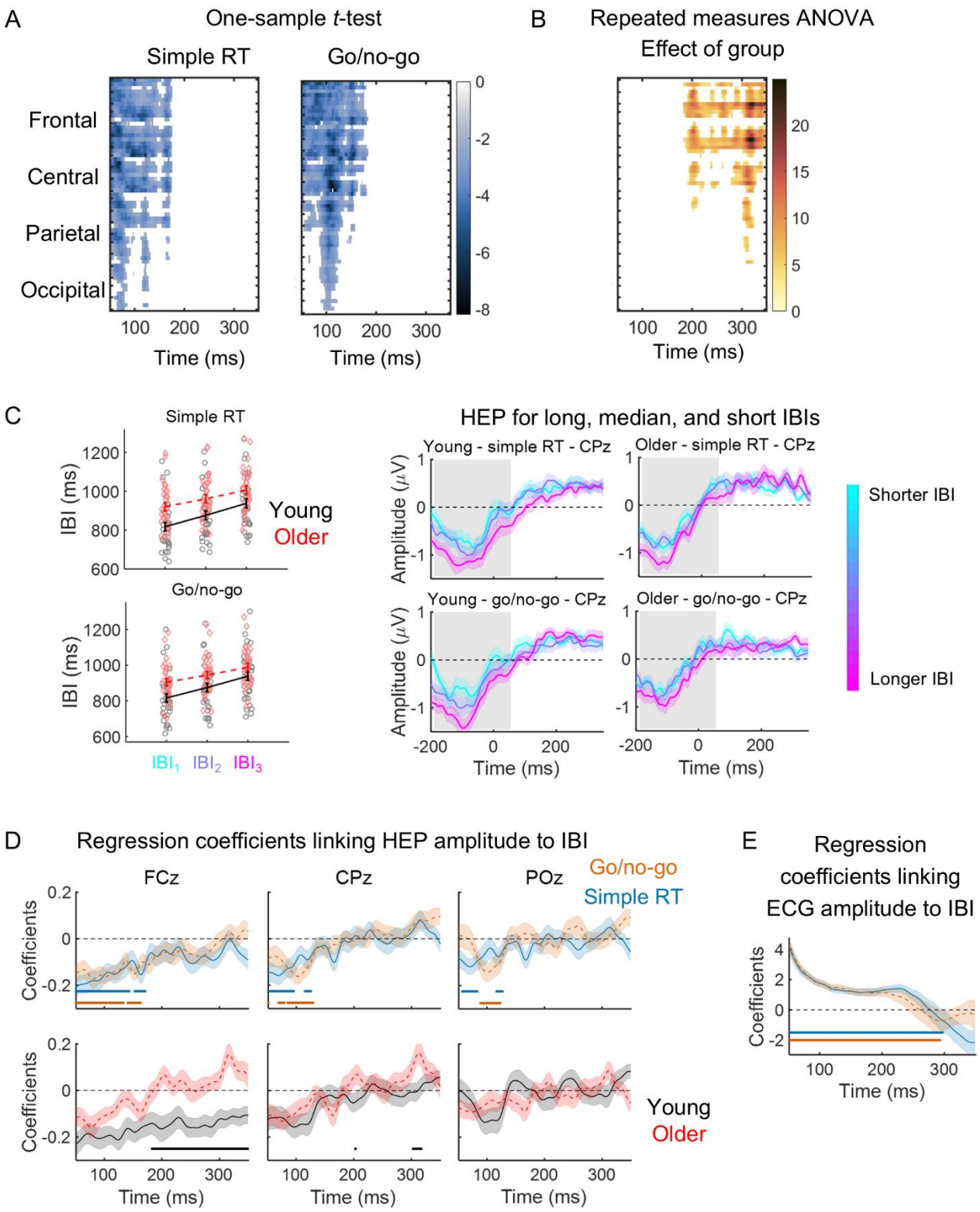

Figure 5. The amplitude of the heartbeat-evoked potential (HEP) is significantly related with cardiac cycle duration [interbeat interval (IBI)]. **(A)** One-sample *t*-test *t*-values within the spatiotemporal cluster where the amplitude of HEP presented a significant linear relation with IBI. **(B)** Repeated measures ANOVA *F*-values within the spatiotemporal cluster where the regression coefficients linking the amplitude of HEP to IBI presented a significant effect of task (left) and a significant effect of group (right). **(A)** and **(B)** EEG channels are stacked up along the y-axis. **(C)** For illustration purposes only, we divided

the HEP within each participant in tertiles according to IBI (represented on the right for the EEG channel CPz). The IBI tertiles are represented in the graph on the left (black continuous line – young group; red dashed line – older group). Longer IBIs (slower heart rate) were associated with a more negative HEP. **(D)** Top row: Time course of the regression coefficients linking HEP amplitude to IBI for the simple RT (blue continuous line) and go/no-go (orange dashed line) task conditions in the midline channels FCz, CPz and POz. The blue and orange horizontal lines indicate the time windows where the coefficients are significantly different from zero (significant temporal clusters from one-sample *t*-tests, $p < .001$). Bottom row: Time course of the regression coefficients linking HEP amplitude to IBI for the young (black continuous line) and older (red dashed line) groups in the midline channels FCz, CPz and POz. The horizontal black line shows the time windows where the coefficients presented a significant effect of group. **(E)** Time course of the regression coefficients linking ECG amplitude to IBI for the simple RT (blue continuous line) and go/no-go (orange dashed line) task conditions. The blue and orange horizontal lines indicate the time windows where the coefficients are significantly different from zero (significant temporal clusters from one-sample *t*-tests, $p < .001$). **(C-E)** Graphs plot the mean across all participants ± standard error of the mean.

To investigate if the observed relationship between cardiac cycle duration and HEP amplitude is a result of signal contamination by the cardiac field artefact, we mimicked the same analysis on the activity recorded on the ECG channel. We found a significant cluster where the regression coefficients were significantly different from zero starting at 51 ms and ending 299 ms after the T peak in the simple RT task and starting at 51 ms and ending 283 ms after the T peak in the go/no-go task condition ($p = .001$; Fig. 5E). We found no significant task effect, no group effect, and no group x task interaction for the coefficients obtained for the ECG data. Thus, the IBI effect at the beginning of the cardiac cycle might reflect some contamination from the electrical cardiac artefact, while the observed group effect suggesting that the effect of IBI on the HEP is stronger in the young group, particularly in frontal channels, is not reflected in differences in the ECG suggesting a neural origin.

IBI at the time of target onset does not predict reaction time

If, as we hypothesized, the HEP interferes with sensorimotor processing and, as our results suggest, HEP amplitude is affected by IBI during task performance, then IBI at the time of target onset might be associated with reaction time. We investigated this hypothesis using within-subject correlation analyses between IBI at the time of target onset and reaction time. At the group level, we tested the correlation coefficients against zero using one-sample *t*-tests for each task and each age group separately. The correlation coefficients were small and not significantly different from zero after controlling for multiple comparisons with Bonferroni correction

(mean ± SD of within subject correlation coefficients: young simple RT = -0.02 ± 0.10; young go/no-go = -0.02 ± 0.17; older simple RT = 0.07 ± 0.15; older go/no-go = -0.03 ± 0.15; one-sample *t*-test: young simple RT $t_{(33)}$ = -1.30, p = .202; young go/no-go $t_{(33)}$ = -.817, p = .429; older simple RT $t_{(30)}$ = 2.41, p = .023; older go/no-go $t_{(30)}$ = -.941, p = .354).

Discussion

In this study, we investigated if changes in cardiac cycle duration (IBI) that occur during the performance of cued reaction time tasks are associated with changes in the neural responses to heartbeats, the HEP. We studied the effect of the anticipatory cardiac deceleration induced by a warning cue (a task-related change in cardiac cycle duration), and the effect of spontaneous fluctuations in cardiac cycle duration not locked with task-relevant events. We studied these responses in young and older adults. The HEP was detectable in young and older participants with no group differences in HEP amplitude or topography during the quiet period of the ECG. We found no evidence that the warning cue induced changes in the HEP in either group of participants. Spontaneous fluctuations in IBI throughout the recordings (not locked to the warning cue) were associated with changes in HEP amplitude, however, we found no evidence of any association between reaction time and IBI at the time of target onset suggesting that the impact of IBI fluctuations on the HEP might not significantly affect sensorimotor processing under our task conditions. However, we did find some evidence of a link between HEP amplitude and reaction time. In the older group, participants with higher HEP amplitude, responded slower in the cued reaction time tasks. Interestingly, this effect was significant in a cluster of EEG channels centred over the left motor cortex. As participants were responding with their right index finger this finding suggests that the HEP amplitude over the motor cortex might be related with the efficiency of motor processing.

The lack of significant group differences in HEP amplitude contrasts with Kamp et al (2021) results that suggested that the HEP was stronger in older than young adults. Visual inspection of the HEP waveforms suggests that the older group presents stronger HEP around the time of the T peak, a time window where the HEP might be contaminated by the cardiac field artefact. Notably, the T peak is delayed in older people (Rabkin et al., 2016; Satpathy et al., 2017) implying differential impact of the cardiac field artefact across age groups. In fact, in Kamp et al. 2021 it was observed that, at an early window after the R peak, group differences are

associated with differences in the ECG. Later group differences around 500 ms after the R peak observed in Kamp et al. (2021) are however not present in our results. This difference in findings could be due to differences in the age range of the participants included (our sample of older participants was on average 10 years younger), cognitive state of the participants (task performance vs rest), or differences in the choice of EEG processing parameters (for example, choice of reference electrode or baseline correction).

The quantification of HEP amplitude and comparison across studies is hindered by the fact that ERP amplitude is affected by the choice of reference electrode and baseline (Coll et al., 2021). Having these limitations in mind, converging evidence suggests that the HEP amplitude changes with the locus of attention, with the modulation of arousal, and with the ability to sense the heart (Coll et al., 2021). HEP amplitude is also modulated by visual stimulation (Sel et al., 2017; Gentsch et al., 2019) and performance outcome (Fouragnan et al., 2022) suggesting that different components of cognitive tasks can have an impact on the neural integration of heartbeats. Paying attention to the heart rhythm appears to increase the amplitude of the HEP in comparison with paying attention to external auditory stimuli (Montoya et al., 1993; Petzschner et al., 2019; Zaccaro et al., 2024). These previous studies observed changes in HEP that occurred during windows of tens of seconds of focused attention. In contrast, we investigated if changes in HEP could be detected during short periods (< 2 s) of focused attention induced by warning cues. These short windows included only one or two cardiac cycles. Under these conditions, we found no change in HEP amplitude in comparison with before the warning cue suggesting that the effect of changes in attention focus on the HEP might only occur following prolonged periods and maybe only detectable when attention changes from internally generated stimuli (interoception) to external sensory stimuli (exteroception).

Another question we were interested in was if HEP amplitude was associated with the speed of sensorimotor processing as assessed by reaction time. We found that older participants with higher HEP amplitude responded slower in the cued reaction time tasks. This relationship was significantly stronger in the older group, was not observed in the young group, and was present in a cluster of electrodes centred on the left motor cortex. As participants were responding with their right index finger, the location of the channels showing a significant association suggests that the HEP interferes with motor related processes. However, a direct link remains to be established as other factors might contribute to differences in HEP amplitude and differences in reaction time explaining the significant relationship. For example, higher HEP amplitude might indicate attentional resources focused inward and therefore slower reaction time to external stimuli. Our finding is, nevertheless, intriguing since cardiac phase and HEP amplitude have been shown to be associated with motor cortex excitability (Ohl

et al., 2016; Kunzendorf et al., 2019; Al et al., 2023; Paci et al., 2024). Unfortunately, we were not able to confirm this association on within-subject analyses because the HEP before and at the time of target onset overlaps with a task related evoked potential, the slow negative potential evoked by the warning cue (the CNV). To control for the effect of this slow evolving potential, we used a baseline correction procedure that works on trial averaged data but will be difficult to apply with precision at the single trial level. Importantly, we have shown before that, within-subject, the CNV amplitude predicts reaction time with more negative CNV amplitudes associated with faster reaction times (Ribeiro and Castelo-Branco, 2022) and therefore this difference in baseline dynamics before the target will affect the estimated HEP amplitude and might induce spurious relationships between apparent HEP amplitude and reaction time. In fact, recently, Steinfath et al. (2024) suggested that the slow changes in baseline associated with preparatory mechanisms and anticipation of a target stimulus might explain some of the previous findings that suggested an association between HEP amplitude and sensory or attentional processes highlighting the need to revisit these concepts (Steinfath et al., 2024). Moreover, in their study they also do not find a relationship between HEP and reaction time after appropriately controlling for baseline shifts.

The warning cue might not induce measurable changes in HEP, but it does induce a significant increase in IBI. It is known that warning cues have a facilitating impact on sensorimotor processing speeding up reaction times (Dietze et al., 2023). Do changes in IBI mediate the effect of the warning cue on reaction time? On our within-subject analysis, we found no evidence that IBI at the time of target onset was associated with reaction time. This is similar to what has been observed in previous studies where cardiac deceleration correlates with reaction time at the between-subjects level but not at the within-subject level (Jennings et al., 1998). Thus, although slower IBIs are thought to facilitate the processing of external sensory signals (Sandman et al., 1977; Skora et al., 2022), in studies using suprathreshold stimuli and reaction time as a proxy for sensorimotor speed, IBI at the time of stimulus onset does not correlate with behaviour. This is in contrast with the fact that the average amplitude of the cue induced cardiac deceleration correlates with average reaction time at between-subjects analyses (Jennings et al., 1998; Reyes et al., 2015; Ribeiro and Castelo-Branco, 2019a). The lack of trial-by-trial correlation indicates that the brain mechanism that induces the cardiac deceleration is associated with reaction time but that the slowdown of the heart itself might not directly affect sensorimotor processing.

Finally, we were interested in the relationship between cardiac cycle duration (IBI) and HEP amplitude. We investigated if fluctuations in IBI were associated with changes in HEP amplitude. Longer IBIs were associated with more negative HEP amplitudes particularly at the early stages of the cardiac cycle before and immediately after the T peak. This effect was significantly reduced in older people, particularly in frontal EEG channels.

However, as, in our tasks, IBI at the time of target onset was not associated with reaction time, this effect of IBI on the HEP does not mediate any obvious effect on task performance.

Limitations

Previous studies investigating the effect of task events on the HEP have observed significant effects with a similar number of trials as in our task (Marshall et al., 2020; Zhang et al., 2023). However, the HEP is an evoked potential with relatively small amplitude and it is possible that only with a larger number of trials an effect of the warning cue could be detected. Nevertheless, it is important to note that Steinfath et al. (2024) using a large number of participants also did not observe a relationship between the HEP and reaction time on a within-subject analysis.

Another limitation of our task design was the relatively small interval between the warning cue and the target. In fact, the peak of the cardiac deceleration occurred after target onset at a time point where we did not evaluate the HEP as it overlaps with target processing mechanisms. It is possible that given longer cue-target intervals associated with stronger cardiac deceleration responses, changes in HEP would become evident. In line with this idea that maybe we did not observe any change in HEP amplitude after the cue because the effect of the cue was associated with a small change in IBI, is the fact that HEP was associated with IBI when we tested this effect using all cardiac cycles. The variability in IBI across all cardiac cycles was two orders of magnitude larger than the change in IBI induced by the cue and appeared to have a strong effect on the HEP. However, at the time points where this relationship was observed, the ECG amplitude was also associated with IBI, and it is possible that this effect reflected, at least in part, contamination by the cardiac field artefact that might have survived signal cleaning during preprocessing.

Finally, to measure the HEP between the cue and the target, it was necessary to correct for the baseline drift induced by the preparatory potential, the CNV. The need to separate these two neural components might have limited our ability to detect subtle changes in the HEP. Future studies might explore other separation methods, for example using ICA to separate the activity from different neural sources (Ribeiro et al., 2016). This method would allow for the study of trial-by-trial variability and its impact on behaviour.

Conclusions

In conclusion, the association and causal link between cardiac function and the processing of incoming sensory stimuli is far from resolved. Our findings appear to suggest that these mechanisms might share a common cause while not being directly linked. It is also possible that a causal mechanism is only revealed in very specific task conditions, for example when processing threshold external sensory stimuli or when changes in cognitive state induce stronger effects on IBI. Future studies should explore these possibilities while taking great care not to confound changes in task-related brain potentials with changes in HEP amplitude by applying appropriate controls and correction methods.

Data and code availability

The dataset used in this study is available in Open Neuro Repository under the https://doi.org/10.18112/openneuro.ds003690.v1.0.0. All analyses and figures presented in the manuscript resulted from analyses of this dataset. MATLAB code for data analyses is available on GitHub on the following link

https://github.com/mariajribeiro/2024_Ribeiro_Effect_of_heart_rate_on_heartbeat-evoked_potential.

Acknowledgments

This work was funded by Fundação para a Ciência e a Tecnologia (SFRH/BPD/102188/2014, EXPL/PSI-GER/0349/2021, FCT/UIDB&P/4950/2020). The funding agency had no involvement in the design of the study, the analysis of the data, writing of the report, or in the decision to submit the article for publication.

Conflict of interest

The authors declare no competing financial interests.

References

Al E, Iliopoulos F, Forschack N, Nierhaus T, Grund M, Motyka P, Gaebler M, Nikulin V V, Villringer A (2020) Heart–brain interactions shape somatosensory perception and evoked potentials. Proc Natl Acad Sci 117:10575–10584 Available at: http://www.pnas.org/lookup/doi/10.1073/pnas.2012463117.

Al E, Iliopoulos F, Nikulin V V., Villringer A (2021) Heartbeat and somatosensory perception. Neuroimage 238:118247 Available at: https://doi.org/10.1016/j.neuroimage.2021.118247.

Al E, Stephani T, Engelhardt M, Haegens S, Villringer A, Nikulin V V. (2023) Cardiac activity impacts cortical motor excitability Gross J, ed. PLOS Biol 21:e3002393 Available at: http://dx.doi.org/10.1371/journal.pbio.3002393.

Azzalini D, Rebollo I, Tallon-Baudry C (2019) Visceral Signals Shape Brain Dynamics and Cognition. Trends Cogn Sci 23:488–509 Available at: https://doi.org/10.1016/j.tics.2019.03.007.

Babo-Rebelo M, Richter CG, Tallon-Baudry C (2016) Neural Responses to Heartbeats in the Default Network Encode the Self in Spontaneous Thoughts. J Neurosci 36:7829–7840 Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.0262-16.2016.

Bellec P, Lavoie-Courchesne S, Dickinson P, Lerch JP, Zijdenbos AP, Evans AC (2012) The pipeline system for Octave and Matlab (PSOM): a lightweight scripting framework and execution engine for scientific workflows. Front Neuroinform 6:1–18 Available at: http://journal.frontiersin.org/article/10.3389/fninf.2012.00007/abstract.

Brainard DH (1997) The Psychophysics Tollbox. Spat Vis 10:433–436.

Coll M-P, Hobson H, Bird G, Murphy J (2021) Systematic review and meta-analysis of the relationship between the heartbeat-evoked potential and interoception. Neurosci Biobehav Rev 122:190–200 Available at: https://doi.org/10.1016/j.neubiorev.2020.12.012.

Delorme A, Makeig S (2004) EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134:9–21.

Dietze N, Recker L, Poth CH (2023) Warning signals only support the first action in a sequence. Cogn Res Princ Implic 8:29 Available at: https://doi.org/10.1186/s41235-023-00484-z.

Fouragnan E, Hosking B, Cheung Y, Prakash B, Rushworth M, Sel A (2022) Timing along the cardiac cycle modulates neural signals of reward-based learning. bioRxiv:1–27 Available at: https://www.embase.com/search/results?subaction=viewrecord&id=L2019769262&from=export%0Ahttp://dx.doi.org/10.1101/2022.07.07.498947.

Freitas S, Simões MR, Alves L, Santana I (2011) Montreal Cognitive Assessment (MoCA): Normative study for the Portuguese population. J Clin Exp Neuropsychol 33:989–996.

Gentsch A, Sel A, Marshall AC, Schütz-Bosbach S (2019) Affective interoceptive inference: Evidence from heart-beat evoked brain potentials. Hum Brain Mapp 40:20–33 Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/hbm.24352.

Gladwin TE, Hashemi MM, van Ast V, Roelofs K (2016) Ready and waiting: Freezing as active action preparation under threat. Neurosci Lett 619:182–188 Available at: http://dx.doi.org/10.1016/j.neulet.2016.03.027.

Hackley S a. (2009) The speeding of voluntary reaction by a warning signal: Presidential Address, 2006. Psychophysiology 46:225–233.

Henriques J, Rocha T, Paredes S, Cabiddu R, Mendes D, Couceiro R, Carvalho P de (2015) ECG Analysis Tool for Heart Failure Management and Cardiovascular Risk Assessment. HIMS'15- Int Conf Heal Informatics Med Syst 2015 Available at: https://pdfs.semanticscholar.org/b7b1/f9033b0884a7a4f3e83c06b8fb07cb9c6a6d.pdf.

Jennings JR, Nebes RD, Yovetich NA (1990) Aging Increases the Energetic Demands of Episodic Memory: A Cardiovascular Analysis. J Exp Psychol Gen 119:77–91.

Jennings JR, van der Molen MW (2005) Preparation for Speeded Action as a Psychophysiological Concept. Psychol Bull 131:434–459.

Jennings JR, van der Molen MW, Steinhauer SR (1998) Preparing the heart, eye, and brain: foreperiod length effects in a nonaging paradigm. Psychophysiology 35:90–98.

Kamp S, Schulz A, Forester G, Domes G (2021) Older adults show a higher heartbeat-evoked potential than young adults and a negative association with everyday metacognition. Brain Res 1752:147238 Available at: https://linkinghub.elsevier.com/retrieve/pii/S0006899320305965.

Kunzendorf S, Klotzsche F, Akbal M, Villringer A, Ohl S, Gaebler M (2019) Active information sampling varies across the cardiac cycle. Psychophysiology 56:e13322 Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/psyp.13322.

Mai S, Wong CK, Georgiou E, Pollatos O (2018) Interoception is associated with heartbeat-evoked brain potentials (HEPs) in adolescents. Biol Psychol 137:24–33 Available at: https://doi.org/10.1016/j.biopsycho.2018.06.007.

Mannina C, Jin Z, Matsumoto K, Ito K, Biviano A, Elkind MSV, Rundek T, Homma S, Sacco RL, Di Tullio MR (2021) Frequency of cardiac arrhythmias in older adults: Findings from the Subclinical Atrial Fibrillation and Risk of Ischemic Stroke (SAFARIS) study. Int J Cardiol 337:64–70 Available at: https://doi.org/10.1016/j.ijcard.2021.05.006.

Marshall AC, Gentsch A, Schütz-Bosbach S (2020) Interoceptive cardiac expectations to emotional stimuli predict visual perception. Emotion 20:1113–1126 Available at: https://doi.apa.org/doi/10.1037/emo0000631.

Montoya P, Schandry R, Müller A (1993) Heartbeat evoked potentials (HEP): topography and influence of cardiac awareness and focus of attention. Electroencephalogr Clin Neurophysiol Potentials Sect 88:163–172 Available at: https://linkinghub.elsevier.com/retrieve/pii/0168559793900016.

Ohl S, Wohltat C, Kliegl R, Pollatos O, Engbert R (2016) Microsaccades Are Coupled to Heartbeat. J Neurosci 36:1237–1241 Available at: https://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.2211-15.2016.

Paci M, Cardellicchio P, Di Luzio P, Perrucci MG, Ferri F, Costantini M (2024) When the heart inhibits the brain: Cardiac phases modulate short-interval intracortical inhibition. iScience 27:109140 Available at: https://doi.org/10.1016/j.isci.2024.109140.

Park H-D, Correia S, Ducorps A, Tallon-Baudry C (2014) Spontaneous fluctuations in neural responses to heartbeats predict visual detection. Nat Neurosci 17:612–618 Available at: https://www.nature.com/articles/nn.3671.

Park H, Blanke O (2019) Heartbeat-evoked cortical responses : Underlying mechanisms , functional roles , and methodological considerations. Neuroimage 197:502–511 Available at: https://doi.org/10.1016/j.neuroimage.2019.04.081.

Pernet CR, Chauveau N, Gaspar C, Rousselet GA (2011) LIMO EEG: A toolbox for hierarchical linear modeling of electroencephalographic data. Comput Intell Neurosci 2011.

Pernet CR, Latinus M, Nichols TE, Rousselet GA (2015) Cluster-based computational methods for mass univariate analyses of event-related brain potentials/fields: A simulation study. J Neurosci Methods 250:85–93 Available at: http://dx.doi.org/10.1016/j.jneumeth.2014.08.003.

Petzschner FH, Weber LA, Wellstein K V., Paolini G, Do CT, Stephan KE (2019) Focus of attention modulates the heartbeat evoked potential. Neuroimage 186:595–606 Available at: https://doi.org/10.1016/j.neuroimage.2018.11.037.

Preacher KJ (2002) Calculation for the test of the difference between two independent correlation coefficients. Available at: http://quantpsy.org.

Rabkin SW, Cheng XBJ, Thompson DJS (2016) Detailed analysis of the impact of age on the QT interval. J Geriatr Cardiol 13:740–748.

Reyes GA, Montoro CI, Duschek S, Reyes GA, Montoro CI, Duschek S (2015) Reaction time , cerebral blood flow , and heart rate responses in fibromyalgia : Evidence of alterations in attentional control Reaction time , cerebral blood flow , and heart rate responses in fibromyalgia : Evidence of alterations in attentional control. J Clin Exp Neuropsychol:414–428.

Ribeiro M, Castelo-Branco M (2022) Slow fluctuations in ongoing brain activity decrease in amplitude with ageing yet their impact on task-related evoked responses is dissociable from behavior. Elife 11:1–28.

Ribeiro MJ, Castelo-Branco M (2019a) Neural correlates of anticipatory cardiac deceleration and its association with the speed of perceptual decision-making, in young and older adults. Neuroimage 199:521–533 Available at: https://linkinghub.elsevier.com/retrieve/pii/S1053811919304896.

Ribeiro MJ, Castelo-Branco M (2019b) Age-related differences in event-related potentials and pupillary responses in cued reaction time tasks. Neurobiol Aging 73:177–189 Available at: https://linkinghub.elsevier.com/retrieve/pii/S0197458018303531.

Ribeiro MJ, Castelo-Branco M (2021) EEG, ECG and pupil data from young and older adults: rest and auditory cued reaction time tasks. OpenNeuro Available at: https://openneuro.org/datasets/ds003690/versions/1.0.0.

Ribeiro MJ, Paiva JS, Castelo-Branco M (2016) Spontaneous Fluctuations in Sensory Processing Predict Within-Subject Reaction Time Variability. Front Hum Neurosci 10:1–15 Available at: http://journal.frontiersin.org/article/10.3389/fnhum.2016.00200.

Rousselet (2011) Modeling single-trial ERP reveals modulation of bottom-up face visual processing by top-down task constraints (in some subjects). Front Psychol 2:1–19 Available at: http://journal.frontiersin.org/article/10.3389/fpsyg.2011.00137/abstract.

Sandman CA, McCanne TR, Kaiser DN, Diamond B (1977) Heart rate and cardiac phase influences on visual perception. J Comp Physiol Psychol 91:189–202 Available at: http://doi.apa.org/getdoi.cfm?doi=10.1037/h0077302.

Satpathy S, Satpathy S, Nayak P (2017) Effect of age and gender on QT interval. Natl J Physiol Pharm Pharmacol 8:1 Available at: http://www.ejmanager.com/fulltextpdf.php?mno=275621.

Sel A, Azevedo RT, Tsakiris M (2017) Heartfelt Self: Cardio-Visual Integration Affects Self-Face Recognition and Interoceptive Cortical Processing. Cereb Cortex 27:5144–5155 Available at: http://cercor.oxfordjournals.org/cgi/doi/10.1093/cercor/bhw296.

Skora LI, Livermore JJA, Roelofs K (2022) The functional role of cardiac activity in perception and action. Neurosci Biobehav Rev 137:104655 Available at: https://doi.org/10.1016/j.neubiorev.2022.104655.

Steinfath P, Herzog N, Fourcade A, Sander C, Nikulin V, Villringer A (2024) Validating genuine changes in Heartbeat Evoked Potentials using Pseudotrials and Surrogate Procedures. bioRxiv:2024.08.24.609348 Available at: http://biorxiv.org/content/early/2024/08/26/2024.08.24.609348.abstract.

Sun Y, Chan KL, Krishnan SM (2005) Characteristic wave detection in ECG signal using morphological transform. BMC Cardiovasc Disord 5:28 Available at: https://bmccardiovascdisord.biomedcentral.com/articles/10.1186/1471-2261-5-28.

Umetani K, Singer DH, McCraty R, Atkinson M (1998) Twenty-Four Hour Time Domain Heart Rate Variability and Heart Rate: Relations to Age and Gender Over Nine Decades. J Am Coll Cardiol 31:593–601 Available at: https://linkinghub.elsevier.com/retrieve/pii/S0735109797005548.

Zaccaro A, della Penna F, Mussini E, Parrotta E, Perrucci MG, Costantini M, Ferri F (2024) Attention to cardiac sensations enhances the heartbeat-evoked potential during exhalation. iScience 27:109586

Available at: https://doi.org/10.1016/j.isci.2024.109586.

Zhang Y, Zhang J, Xie M, Ding N, Zhang Y, Qin P (2023) Dual interaction between heartbeat-evoked responses and stimuli. Neuroimage 266:119817 Available at: https://doi.org/10.1016/j.neuroimage.2022.119817.