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Cardiac Cycle Phase Modulates Pain Processing During Heartbeat-Enhanced Rubber Hand Illusion

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ABSTRACT

Pain—a complex, highly subjective experience—is shaped by interoceptive signals, especially the systolic and diastolic phases of cardiac rhythmicity. While body ownership illusions (BOI, the perceptual attribution of artificial limbs to one's own body) are modulated by interoceptive signals, their influence on pain processing remains controversial, with conflicting findings in the literature. Critically, it remains unclear whether cardiac-phase-specific pain modulation occurs independently of BOI. To resolve this, we examined: (1) the effects of cardiac cycles, (2) the influence of BOI, and (3) their potential interactions on pain processing. In the present study, we used a virtual reality rubber hand illusion (VR-RHI) paradigm to induce BOI. In the control condition (object, OBJ condition), participants viewed a VR scenario with an inanimate object (cardboard) instead of a rubber hand, which does not induce BOI. Pain stimulation was administered under four experimental conditions: RHI-systole, RHI-diastole, OBJ-systole, and OBJ-diastole. We assessed pain perception—thresholds, intensity and unpleasantness ratings, and somatosensory evoked potentials (SEPs)—while delivering painful electrical stimuli timed to systolic or diastolic phases under BOI and control VR conditions. Results demonstrated that compared to the systolic phase, the diastolic phase was associated with significantly lower pain intensity and unpleasantness ratings, along with reduced SEP amplitudes. However, neither BOI nor its interaction with cardiac cycle exerted significant effects on these measures. Our findings suggest that while cardiac cycle modulates pain perception, this effect operates independently of BOI.

1 | Introduction

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (Raja et al. 2020). As a complex and subjective phenomenon, pain is modulated by multiple sensory inputs, with interoception gaining increasing recognition as a critical factor (Horsburgh et al. 2024). Interoception refers to the perception of internal physiological states, such as hunger, temperature, and heart rate (Craig 2003; Tsakiris et al. 2011). Among interoceptive signals, heartbeat perception has been the most extensively studied and is considered one of the most reliable measures (Brener and Ring 2016). The electrical activity within the heart maintains a rhythmic pattern, as electrical impulses travel through the cardiac muscle, triggering contractions that push blood out of the aorta and regulate heartbeat (Ma et al. 2017). Functioning as an oscillator, the heart undergoes two phases: diastole, characterized by ventricular filling, and systole, marked by blood ejection. Together, these phases constitute a complete cardiac cycle.

Research exploring the temporal relationship between heartbeats and external stimuli has demonstrated that auditory (Van Elk et al. 2014), visual (Salomon et al. 2016), or painful (McIntyre et al. 2006) stimuli are attenuated when synchronized with cardiac activity. Prior research has shown that the timing of painful stimuli relative to the cardiac cycle significantly modulates pain perception. For example, several studies have reported higher pain thresholds during systole compared to diastole (Edwards et al. 2001, 2002; Wilkinson et al. 2013). To explain this phenomenon, researchers have proposed the pulsed inhibition hypothesis, which posits that activation of carotid sinus baroreceptors during systole transiently suppresses cortical activity, leading to pain attenuation (Dworkin et al. 1994; Skora et al. 2022; Motyka et al. 2019; Al et al. 2020). However, opposite results have been reported for unpredictable pain and emotional stimuli, with subjective ratings being enhanced during systole compared to diastole (Martins et al. 2009; Garfinkel et al. 2014, 2021). In particular, Martins et al. (2009) found that both pain intensity and unpleasantness ratings peaked for stimuli presented at 300 ms after the R-wave of the electrocardiogram (ECG). Martins et al. attributed these cardiac phase effects to the stimulus unpredictability inherent in their mixed blocked design. Critically, converging evidence indicates that high-level cognitive operations exhibit systolic hypersensitivity. For instance, stereotype activation demonstrates greater salience when processed during systole (Azevedo, Badoud, and Tsakiris 2017).

Pain comprises sensory, cognitive, and affective dimensions (Raja et al. 2020). Pain perception is deeply intertwined with the sense of body ownership (Martini 2016), as both are believed to stem from multisensory integration processes (Coppi et al. 2024; Crucianelli et al. 2024). The sense of body ownership is predominantly studied through the RHI, in which the synchronous, but not asynchronous, stroking of an individual's hidden real hand and a false rubber hand in an anatomically congruent position can induce the feeling that the rubber hand is part of one's own body (Botvinick and Cohen 1998; Ehrsson et al. 2004). The subjective experience of a rubber hand or body part as being one's own is referred to as the BOI (Ehrsson 2012; Matamala-Gomez et al. 2021). Notably, BOIs can also be induced when participants experience their actual body being replaced by a virtual body in a VR environment (Slater et al. 2009; Mottelson et al. 2023).

BOI's analgesic promise is unsettled: some studies find heightened pain tolerance under the illusion (Hegedüs et al. 2014; Fang et al. 2019; Pamment and Aspell 2017), whereas others report increased pain (Siedlecka et al. 2018) or null effects (Mohan et al. 2012; Gong et al. 2022). These contradictions often trace back to procedural nuance—e.g., Siedlecka et al. (2018) masked visual feedback, amplifying stimulus uncertainty and pain ratings. Distance between real and virtual hands also matters (Nierula et al. 2017). Extending the paradigm, Suzuki et al. (2013) synchronized red flashes with each heartbeat, forging a "cardiac rubber-hand illusion" that deepens embodiment by marrying cardiac rhythm with visual cues.

Electroencephalography (EEG) recordings provide high temporal resolution for analyzing pain-related neural activity, as reflected in SEPs induced by transcutaneous electrical nerve stimulation using surface electrodes (Cruccu et al. 2008; Hird et al. 2018). In pain studies, electrocutaneous stimuli typically elicit two key SEP components: (1) an early negative deflection (100–140 ms) localized to contralateral SI/SII cortices, reflecting initial sensory processing and (2) a later vertex-positive wave (~200 ms) associated with anterior cingulate activity, marking cognitive aspects of pain perception (Fiorio et al. 2012; Clauwaert et al. 2018). These components collectively enable investigation of both sensory-discriminative and affective dimensions of pain.

By integrating RHI and VR, the primary aim of the current study was to systematically examine whether cardiac cycle phases (systole vs. diastole) modulate pain processing, as assessed through subjective ratings of pain intensity and unpleasantness, and SEPs. Building on the pulsed inhibition hypothesis, we predicted that painful stimuli administered during cardiac systole would elicit significantly lower pain intensity ratings, reduced unpleasantness, and attenuated SEP amplitudes compared to diastolic-phase stimulation. We developed a heartbeat-enhanced VR-RHI paradigm that combines cardio-visual stimulation with immersive VR technology to optimize BOI strength. We hypothesize that the RHI condition will produce significant analgesic effects compared to the OBJ control condition. As a secondary objective, this study aims to investigate whether BOI modulates pain processing within this heartbeat-enhanced VR-RHI paradigm. Therefore, the present study utilizes the heartbeat-enhanced VR-RHI paradigm to investigate: (1) the distinct contributions of cardiac cycle phases (systole vs. diastole) and (2) the effects of BOI (RHI vs. OBJ) on pain processing, while incorporating real-time cardiac recording and visualization.

2 | Methods

2.1 | Participants

Thirty-four healthy participants (16 female; mean age = 22.14; SD = 2.75, range: 19–27 years) attended this study. All participants met the following inclusion criteria: (1) normal or corrected-to-normal vision, (2) no history of hearing impairment, (3) no diagnosed mental or neurological disorders, (4) no current pain conditions or substance use. Female participants were instructed to participate during non-menstruating periods to control for potential menstrual cycle effects on pain perception (Grandi et al. 2012). The sample size was determined a priori using G*Power 3.1 software (Version 3.1.9.7, Düsseldorf, Germany) (Faul et al. 2007) for a repeated-measures F test. Based on an estimated medium effect size ($f = 0.25$), $\alpha = 0.05$, and power $(1-\beta) = 0.9$, the analysis indicated a required sample size of 30 participants to detect significant within-subjects effects. The study protocol was approved by the Academic Affairs Committee of the School of Psychological and Cognitive Sciences at Peking University. All participants provided written informed consent after receiving a complete description of study procedures. While participants were informed that the study investigated pain perception, specific hypotheses were not disclosed to prevent expectancy effects. Participants received monetary compensation for their time

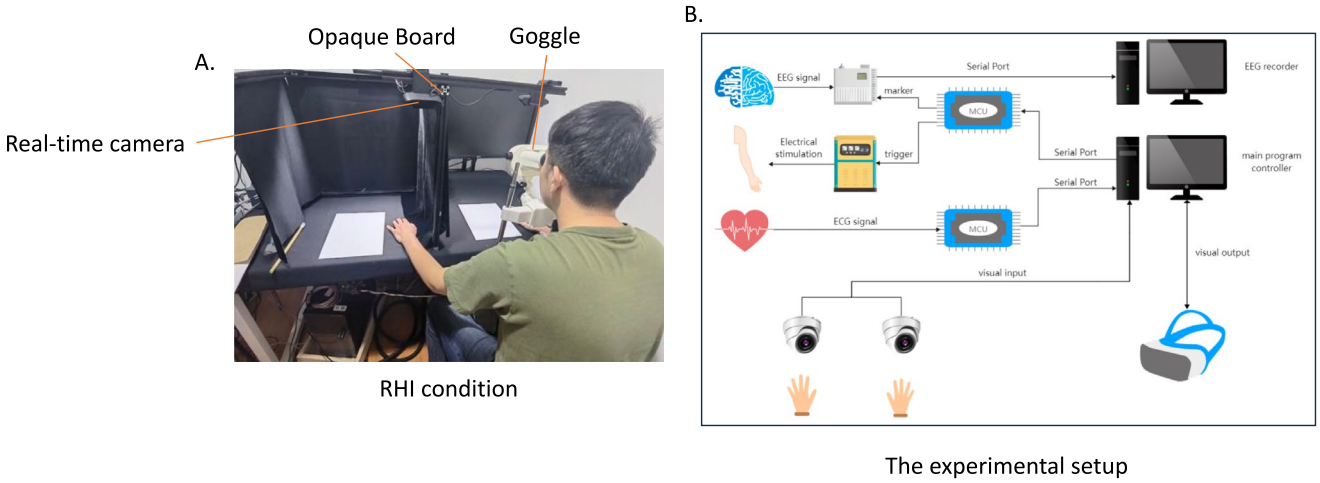

FIGURE 1 | Experimental setup and design. (A) Participants were seated at a testing table with both hands maintained in standardized positions. A camera continuously captured the participant's left hand, generating a real-time 3D virtual representation that was rendered in the goggles. (B) The experimental setup employed two custom single-chip MCUs for integrated device control: One MCU was dedicated to real-time ECG signal acquisition and R-wave detection using a validated algorithm, while the second MCU coordinated stimulus delivery and synchronization. Upon R-wave detection, the system triggered phase-specific visual feedback (a 200-ms red light pulse delivered through VR goggles) and, during the pain processing phase, generated precisely timed trigger pulses to both the electrical stimulator and EEG acquisition system with a temporal jitter of <2 ms. This dual-MCU architecture ensured millisecond-level synchronization between cardiac events, visual stimuli, and pain stimulation, while maintaining precise alignment with EEG event markers throughout all experimental conditions.

and were advised of their right to withdraw from the study without penalty at any point.

2.2 | Apparatus

The experimental configure is illustrated in Figure 1. Each participant was seated on a chair with both arms resting comfortably on a standardized platform (Figure 1A). An opaque board prevented visual access to the participant's left arm. Arm positioning was standardized using anatomical markers to maintain a fixed 45 cm inter-arm distance. Head position was stabilized using a custom-designed chin rest with adjustable height. Visual stimuli were presented through high-resolution LCD goggles (NordicNeuroLab, Bergen, Norway), with the virtual left hand consistently positioned 20 cm lateral to the sagittal midline across all experimental conditions to maintain spatial standardization.

For cardiac signal visualization, we implemented a real-time feedback system displaying both systolic and diastolic phases with millisecond precision. The hardware architecture comprised two customized single-chip microcontrollers (MCUs) for device integration: one dedicated to ECG signals acquisition, and the other for sending synchronization markers and triggers to the EEG acquisition system and electrical stimulator. ECG was recorded using a three-electrode configuration with disposable Ag/AgCl electrodes. EEG data were acquired through a 64-channel active electrode system. Both MCUs interfaced with the main control program via serial communication, which centralized all experimental logic. Upon detecting an ECG R-wave, the program triggered peripheral devices and provided phase-specific visual feedback based on experimental conditions. The MCU ensured precise temporal synchronization by simultaneously delivering trigger pulses to both the electrical pain stimulator and the EEG acquisition system. This approach guaranteed accurate alignment between painful stimulus delivery and corresponding event markers in the EEG recordings (Figure 1B).

2.3 | BOI Induction

In the VR-RHI condition, both hands of the participants were positioned within the field of view, as illustrated in Figure 2A. The experimenter stood behind the participants during the experiment. To induce the illusion, the participant's real left hand was gently stroked with a paintbrush 30 times over a 2-min duration, accompanied by visual feedback presented through the goggles. Throughout this test, participants were instructed to maintain visual fixation on the left virtual hand. For the VR-OBJ condition, the virtual hand was replaced with a cardboard object ($22\times10\times0.5$ cm) positioned at identical spatial coordinates to the virtual hand location in the RHI condition (Figure 2B). The cardboard was placed in the same location as the participant's real left hand in the VR-RHI condition. Similar to the VR-RHI condition, the participant's hidden left hand was also stroked 30 times over 2 min.

2.4 | Detection of Heartbeat and Cardio-Visual Feedback

Disposable Ag/AgCl ECG electrodes were placed on the participant's right arm, left arm, and left leg. The MCUs continuously monitored the ECG signal and detected R-waves in real time. Each detected R-wave triggered a visual pulse (200 ms in duration) locked to the cardiac cycle: at 300 ms post-R-wave

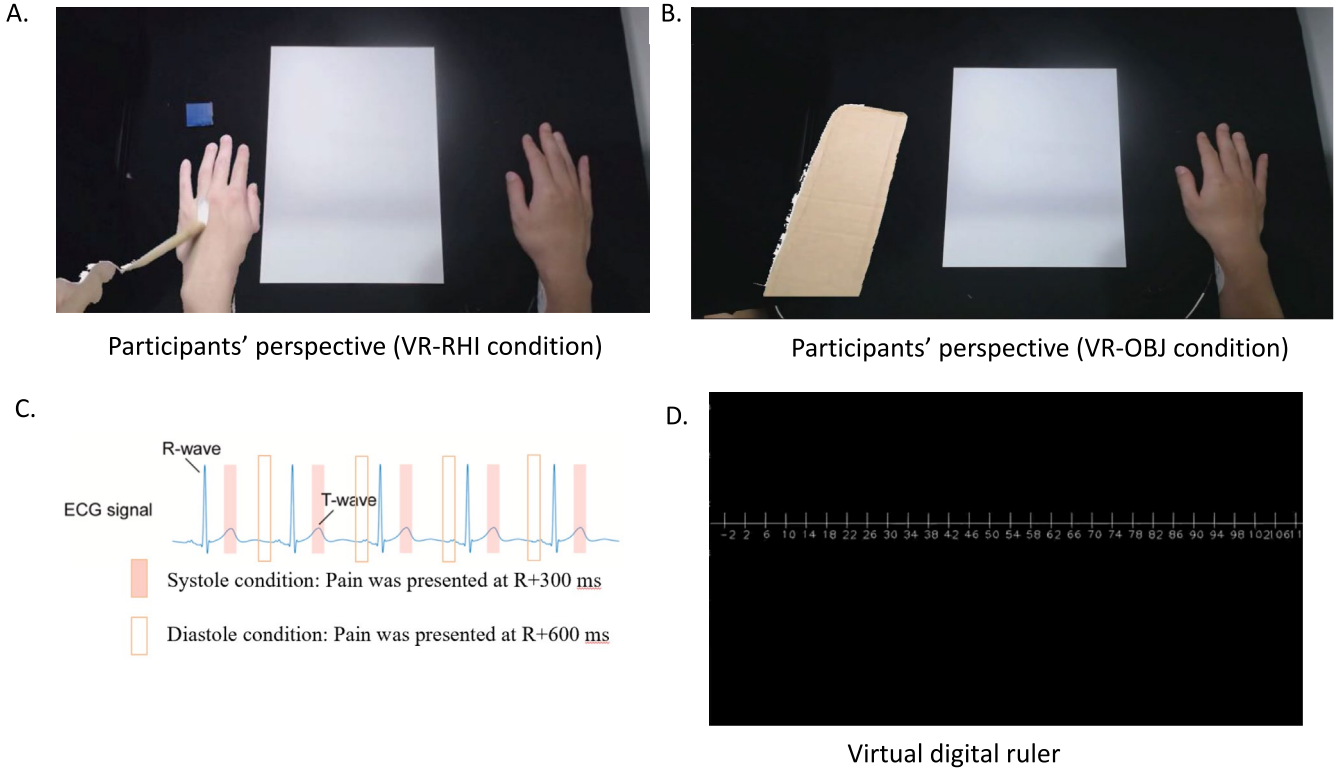

FIGURE 2 | (A) In the OBJ condition, participants observed their own right hand alongside a virtual cardboard object. (B) In the RHI condition, participants viewed their physical right hand paired with a spatially aligned virtual representation of their left hand (intermanual distance: 40 cm) through the goggles. They received standardized instructions to maintain continuous visual fixation on the virtual left hand. (C) The visual feedback stimuli and painful stimuli were both precisely time-locked to distinct cardiac phases, with systole-triggered presentations occurring 300 ms post-R-wave and diastole-triggered presentations delivered 600 ms post-R-wave. (D) During pre- and post-testing for each experimental condition, participants provided verbal reports of their perceived left hand's position by indicating the numerical value aligned with their left index finger on a visually presented virtual ruler.

the entire virtual hand—substituted by a cardboard object in control trials—flashed red to mark systole, whereas at 600 ms the same flash signaled diastole (Figure 2C). A crisp 200-ms flash—uniform across trials—delivered a time-locked visual heartbeat.

2.5 | Pain Threshold and the Intensity of Painful Stimulus

Pain perception was assessed through standardized threshold measurement and subjective ratings of stimulus intensity and unpleasantness. Electrical pain stimuli were delivered via a pair of disposable Ag/AgCl electrodes (1 cm inter-electrode distance) positioned on the volar aspect of the left distal forearm, located 2 cm proximal to the wrist. Single 2-ms electric square-wave pulses were delivered by a constant-current stimulator with a maximum voltage of 400 V (DS7A; Digitimer Ltd., Welwyn Garden City, UK).

Pain thresholds were determined separately for each of the four experimental conditions using an 11-point numerical verbal rating scale (NRS; 0 = "no sensation" to 10 = "most intense pain imaginable"). The stimulation intensity began at 0 mA and increased in 0.5 mA increments until participants reported a rating of 4 ("just noticeable pain"), which operationally defined their pain threshold. During experimental trials, the stimulation intensity was maintained at each participant's individualized pain threshold plus 1 mA to ensure consistent suprathreshold pain perception across conditions while minimizing habituation effects (Klein et al. 2004).

2.6 | BOI Assessment

BOI was quantitatively assessed using two complementary measures: proprioceptive drift and responses to RHI questionnaire.

2.6.1 | Proprioceptive Drift

For the proprioceptive drift test, participants viewed a virtual ruler (shown in Figure 2D) through the goggles before and after each experimental condition (Tsakiris and Haggard 2005; Suzuki et al. 2013). They were instructed to verbally report the numerical value aligned with the tip of their left index finger, which corresponded to the perceived location of their left hand. The proprioceptive drift was calculated as the difference (in centimeters) between the pre- and post-experiment position estimates. To prevent memorization of numerical values, the ruler's scale was randomized across trials while maintaining consistent spatial intervals between scale markers.

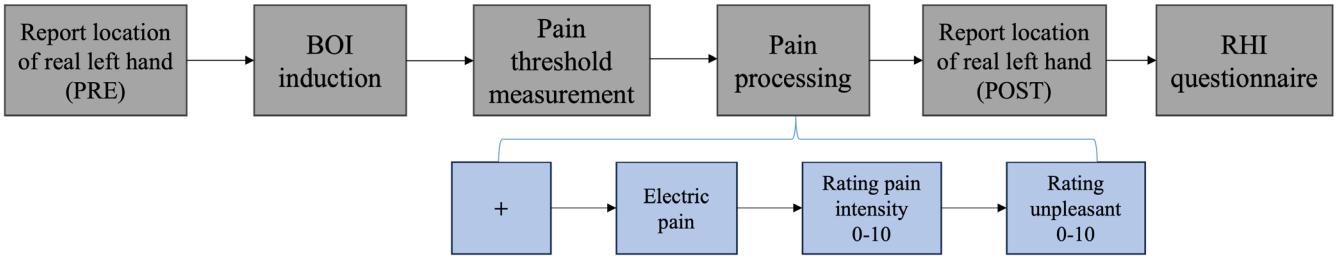

FIGURE 3 | Schematic representation of the experimental protocol as well as the typical trial sequence for the pain processing session. Participants first estimated the position of their left hand on a virtual ruler, followed by a BOI induction phase, after which pain thresholds were measured. This was followed by a pain processing phase in which participants were shown "+" to remind attention and then received a pain stimulus, followed by ratings of the intensity and unpleasantness of the pain stimuli, while EEG of the pain stimulus was recorded. After the pain processing phase, participants again estimated the position of their left hand on a virtual ruler. Finally, the RHI questionnaire was completed.

2.6.2 | RHI Questionnaire

Following each experimental condition, participants completed an 11-item questionnaire assessing both BOI and cardiac awareness. The questionnaire incorporated items adapted from Solcà et al. (2018), with Q1–Q5 and Q7–Q11 drawn from their validated measures, while Q6 was specifically designed to assess perceived spatial congruence between the real and virtual hands (full questionnaire available in Supporting Information). Responses were recorded using a 7-point Likert scale (0 = "strongly disagree" to 6 = "strongly agree").

2.7 | Experimental Design

The study employed a 2 (BOI: RHI, OBJ) × 2 (cardiac cycle: systole [sys], diastole [dia]) within-participants design. The VR-RHI paradigm served as our primary experimental manipulation. In the VR-RHI condition, we induced a robust BOI through synchronous visuotactile stimulation, while the VR-OBJ control condition does not typically elicit ownership experiences (see Section 2.4 for detailed procedures). The second independent variable involved precisely timed delivery of painful stimuli at specific cardiac cycle phases: Systolic phase, stimuli delivered 300 ms post R-wave; diastolic phase, stimuli delivered 600 ms post R-wave.

2.8 | Experimental Procedure

Upon arrival, participants signed the informed consent form. Each participant was seated with their chin stabilized in a customized 3D-printed headrest, wearing VR goggles, and with both hands positioned according to the experimental protocol. The procedure consisted of the following sequential phases: First, participants were presented with a virtual ruler displaying randomized and sequentially incremented numerical values. They estimated the spatial position of their left hand by reporting the numeric value aligned with the tip of their index finger. This was followed by a 2-min BOI induction period, after which individual pain thresholds were determined using the protocol described in Section 2.6. Subsequently, a pain processing phase ensued, consisting of 30 trials per condition. At the beginning of each trial, participants were presented with a cross to remind them to maintain their attention. Painful electrical stimuli were administered at random intervals within a 10-s window following fixation offset, with stimulation parameters set according to individual thresholds (see Section 2.6). Participants rated the intensity and unpleasantness of the painful stimulation separately. Continuous EEG was recorded throughout the pain processing phase (Figure 3). Following the pain processing trials, post-test proprioceptive drift was assessed by verbal report of the virtual ruler value aligned with the left index fingertip. Finally, participants completed a standardized RHI questionnaire at the end of each block. To minimize potential respiratory influences on experimental measures, participants underwent a 10-min standardized resting period prior to testing to ensure stabilization of physiological baselines, and received explicit instructions to maintain natural, unpaced breathing throughout all experimental procedures. The experiment employed a fully counterbalanced block design with four conditions (2 BOI conditions × 2 cardiac phases), with condition order randomized across participants. Illustration of the RHI setup is provided in Video S1.

2.9 | EEG Recording and Preprocessing

Continuous EEG data was recorded using the 64-electrode actiCAP active electrode system from Brain Products (Munich, Germany) with a sampling rate of 1000 Hz. The EEG montage incorporated a dedicated infraorbital electrode positioned below the right eye to record vertical electrooculographic (vEOG) activity, enabling systematic identification and removal of ocular artifacts during subsequent preprocessing. The ground electrode was positioned at AFz, and the reference electrode was positioned at FCz. All electrode impedances were maintained below 10 KΩ to ensure optimal signal quality. Data were recorded using BrainVision Recorder software (Version 1.21, Brain Products) with an analog bandpass filter of 0.1–100 Hz.

We conducted offline EEG analysis using customized MATLAB functions and the EEGLAB Toolbox for MATLAB (Delorme and Makeig 2004). Initially, the signals were down-sampled to 500 Hz and re-referenced to the mean of the left and right mastoids. Subsequently, a band-pass filter with a range of 1–30 Hz was applied. EEG epochs were extracted using a 720 ms window, spanning from 120 ms prior to electrical painful stimulus

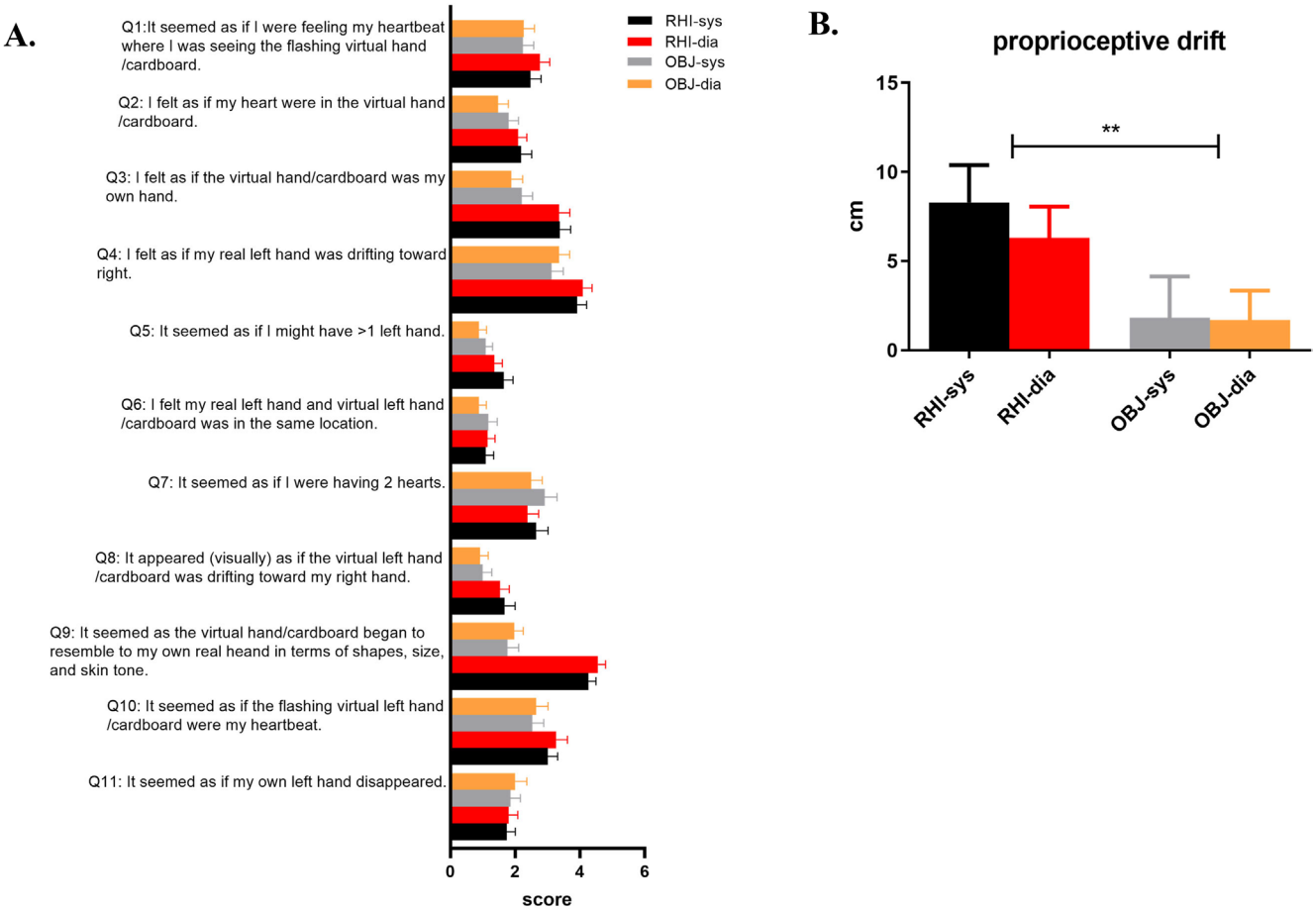

FIGURE 4 | (A) Results for each item in the scale under four conditions. (B) Results of proprioceptive drift under four conditions. $^{**}p < 0.01$.

onset to 600 ms following it. The average amplitude from −120 to 0 ms served as the baseline for normalizing the average signals. Obvious artifacts, such as saccades, blinks, cardiovascular signals, and tonic muscle sounds, were manually removed using independent component analysis.

2.10 | Data Analysis

Drawing from the existing literature and visual examination of our data (Clauwaert et al. 2018; Ladouceur et al. 2018), two components were identified: an early negative component around 120 ms (i.e., N1) and a later positive component around 200 ms (i.e., P2). The mean amplitude within specific time windows was extracted for further analysis. Specifically, the mean amplitude between 110 and 130 ms at the contralateral primary sensory cortex (F4, FC4, F6, FC6 electrodes) and between 180 and 300 ms at the parietal cortex (C1, Cz, C2 electrodes) was selected for each participant across all conditions.

We conducted a comparative analysis of the painful threshold, intensity rating, unpleasant rating, BOI, and SEPs (N1 and P2) amplitudes across the four experimental conditions. We performed two-way repeated measures ANOVAs, with the factors of BOI (RHI, OBJ) and cardiac cycle (systole, diastole) as within-participants factors. We analyzed behavioral data with SPSS 22.0 (SPSS Software, Armonk, NY, USA) and GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA). The criterion for statistical significance was set at $p < 0.05$. In cases where the assumption of sphericity was violated, a Greenhouse–Geisser correction was applied. Post hoc tests were adjusted using the Bonferroni correction.

3 | Results

3.1 | BOI

For each item of the questionnaire (Figure 4A), a significant main effect of BOI was observed in item 3 [F (1,33) = 13.02, $p < 0.01$, $\eta_p^2 = 0.28$], item 4 [F (1,33) = 5.65, $p < 0.05$, $\eta_p^2 = 0.14$], item 8 [F (1,33) = 5.09, $p < 0.05$, $\eta_p^2 = 0.13$], and item 9 [F (1,33) = 96.59, $p < 0.01$, $\eta_p^2 = 0.74$]. However, the main effect of cardio-cycle and the interaction effect between BOI and cardio-cycle did not reach significance (all $ps > 0.05$). There was no significant effect of the main effect of BOI, cardio-cycle, and the interaction effect of them in items 5, 6, and 11 (all $ps > 0.05$).

For the proprioceptive drift (Figure 4B), a significant main effect of BOI was found, F (1,33) = 7.22, $p < 0.05$, $\eta_p^2 = 0.18$, with larger proprioceptive drift in RHI trials ($M = 7.29$, SE = 1.68) than in OBJ trials ($M = 1.77$, SE = 1.76). The main effect of cardio-cycle and the interaction between BOI and cardio-cycle did not reach significance (all $ps > 0.05$). Across two cardio-cycle

TABLE 1 | Pain threshold, intensity rating, and unpleasant rating results.

Variables	Pain threshold			Intensity rating			Unpleasant rating		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
BOI	0.22	0.64	0.01	0.39	0.54	0.01	0.06	0.81	0.00
Cardio-cycle	0.54	0.47	0.02	8.08	**< 0.01**	0.20	8.29	**< 0.01**	0.20
BOI × cardio-cycle	0.32	0.58	0.01	0.74	0.40	0.02	0.18	0.68	0.01

Note: Significance of bold values represents the statistical significance of *p* values when $p < 0.01$.

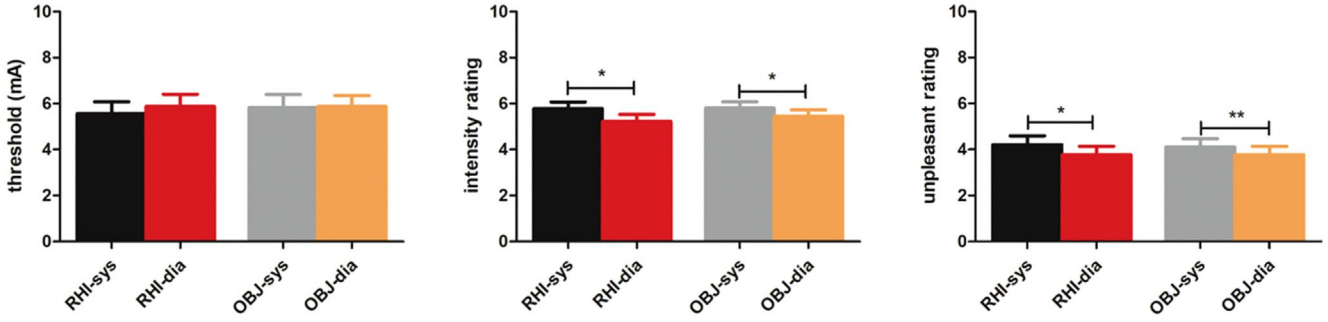

FIGURE 5 | Results showing threshold, intensity rating, and unpleasant rating in the four experimental conditions. *$p < 0.05$ and **$p < 0.01$.

conditions, proprioceptive drift in the RHI trials was larger than in OBJ trials, $M_{RHI\text{-}sys} = 8.29$, $SE_{RHI\text{-}sys} = 2.08$; $M_{OBJ\text{-}sys} = 1.82$, $SE_{OBJ\text{-}sys} = 2.31$; $M_{RHI\text{-}dia} = 6.29$, $SE_{RHI\text{-}dia} = 1.76$; $M_{OBJ\text{-}dia} = 1.70$, $SE_{OBJ\text{-}dia} = 1.63$.

3.2 | Pain Perception

The results for pain threshold, intensity rating, and unpleasant rating were shown in Table 1 and Figure 5. For pain threshold, the main effect of BOI and cardio-cycle, and their interaction were not significant (all $ps > 0.05$, $M_{RHI\text{-}sys} = 5.55$, $SE_{RHI\text{-}sys} = 0.52$; $M_{OBJ\text{-}sys} = 5.82$, $SE_{OBJ\text{-}sys} = 0.57$; $M_{RHI\text{-}dia} = 5.86$, $SE_{RHI\text{-}dia} = 0.53$; $M_{OBJ\text{-}dia} = 5.86$, $SE_{OBJ\text{-}dia} = 0.48$).

For pain intensity, a significant main effect of cardio-cycle was observed, $F(1, 33) = 8.90$, $p < 0.01$, $\eta_p^2 = 0.20$, with higher scores being observed in systole trials ($M = 5.54$, $SE = 0.27$) than in diastole trials ($M = 5.14$, $SE = 0.24$). However, the main effect of BOI and the interaction between BOI and cardio-cycle were not statistically significant (all $ps > 0.05$). Across two BOI conditions, pain intensity ratings in the systole trials were higher than in diastole trials, $M_{RHI\text{-}sys} = 5.50$, $SE_{RHI\text{-}sys} = 0.31$; $M_{OBJ\text{-}sys} = 5.57$, $SE_{OBJ\text{-}sys} = 0.28$; $M_{RHI\text{-}dia} = 5.04$, $SE_{RHI\text{-}dia} = 0.28$; $M_{OBJ\text{-}dia} = 5.22$, $SE_{OBJ\text{-}dia} = 0.25$.

Regarding the results of unpleasant rating, a significant main effect of cardio-cycle was found, $F(1, 33) = 10.58$, $p < 0.01$, $\eta_p^2 = 0.24$, with higher scores being reported in systole trials ($M = 3.96$, $SE = 0.36$) than in diastole trials ($M = 3.59$, $SE = 0.36$). However, the main effect of BOI and the interaction between BOI and cardio-cycle were not statistically significant (all $ps > 0.05$). Across two BOI conditions, unpleasant ratings in the systole trials were higher than in diastole trials, $M_{RHI\text{-}sys} = 3.98$, $SE_{RHI\text{-}sys} = 0.38$; $M_{OBJ\text{-}sys} = 3.92$, $SE_{OBJ\text{-}sys} = 0.36$; $M_{RHI\text{-}dia} = 3.48$, $SE_{RHI\text{-}dia} = 0.38$; $M_{OBJ\text{-}dia} = 3.69$, $SE_{OBJ\text{-}dia} = 0.36$.

TABLE 2 | N1 and P2 results.

Variables	N1			P2		
	F	*p*	η_p^2	*F*	*p*	η_p^2
BOI	0.02	0.89	0.01	0.34	0.57	0.01
Cardio-cycle	6.08	**< 0.05**	0.16	9.25	**< 0.01**	0.22
BOI × cardio-cycle	0.05	0.83	0.00	0.18	0.67	0.01

Note: Significance of bold values represents the statistical significance of *p* values when $p < 0.05$; $p < 0.01$.

3.3 | SEPs

The results of SEPs were shown in Table 2 and Figure 6. For N1, a significant main effect of cardio-cycle was observed, $F(1, 33) = 6.08$, $p < 0.05$, $\eta_p^2 = 0.16$, with more negative wave in systole trials ($M = -8.08$, $SE = 1.13$) than in diastole trials ($M = -6.49$, $SE = 0.99$). However, the main effect of BOI and the interaction between BOI and cardio-cycle yielded no statistically significant results (all $ps > 0.05$). Under the RHI conditions, the N1 was more negative in systole trials than in diastole trials, but the difference between systole and diastole was not significant ($p = 0.06$) under the OBJ conditions, $M_{RHI\text{-}sys} = -8.17$, $SE_{RHI\text{-}sys} = 1.13$; $M_{OBJ\text{-}sys} = -7.98$, $SE_{OBJ\text{-}sys} = 1.28$; $M_{RHI\text{-}dia} = -6.50$, $SE_{RHI\text{-}dia} = 1.16$; $M_{OBJ\text{-}dia} = -6.48$, $SE_{OBJ\text{-}dia} = 1.00$.

Regarding the results of P2, a significant main effect of cardio-cycle was found, $F(1, 33) = 9.25$, $p < 0.01$, $\eta_p^2 = 0.22$, with larger amplitude in systole trials ($M = 19.03$, $SE = 1.41$) than in diastole trials ($M = 17.20$, $SE = 1.18$). However, the main effect of BOI and the interaction between BOI and cardio-cycle were not statistically significant (all $ps > 0.05$). The amplitude of P2 was larger in systole trials than in diastole trials under both BOI conditions, $M_{RHI\text{-}sys} = 18.81$, $SE_{RHI\text{-}sys} = 1.45$; $M_{OBJ\text{-}sys} = 19.24$,

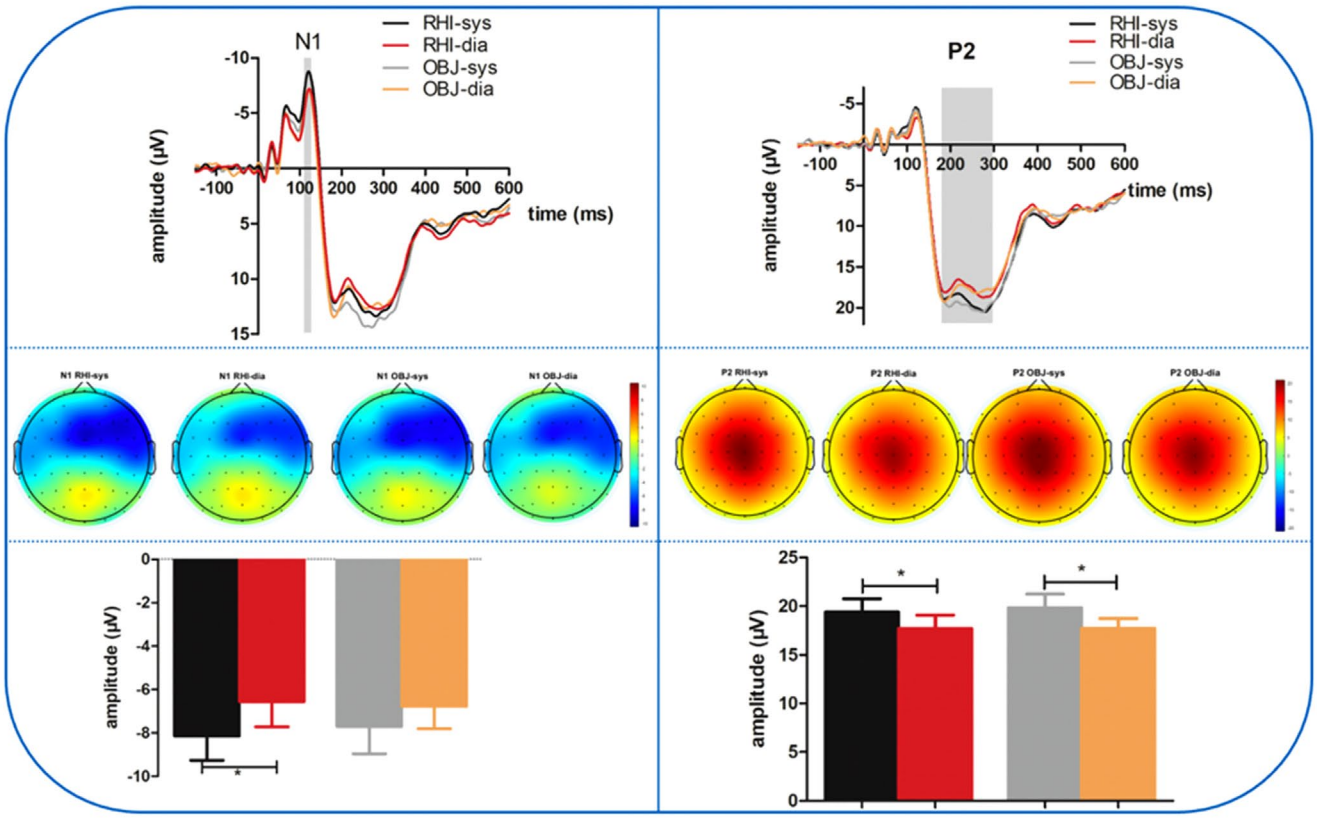

FIGURE 6 | Comparison of SEPs across four experimental conditions.

$SE_{OBJ\text{-}sys} = 1.49; M_{RHI\text{-}dia} = 17.18, SE_{RHI\text{-}dia} = 1.42; M_{OBJ\text{-}dia} = 17.22, SE_{OBJ\text{-}dia} = 1.10.$

4 | Discussion

In this study, we investigated the impact of the cardiac cycle and BOI on pain processing using a heartbeat enhanced VR-RHI paradigm. Our results reveal three key findings: First, we observed significant cardiac cycle-dependent modulation of pain perception, with attenuated pain processing during diastole compared to systole. Second, this cardiac modulatory effect occurred independently of BOI induction. Third, the experimental manipulation of BOI failed to significantly influence pain perception, as assessed through both subjective ratings and electrophysiological measures.

The current findings demonstrated a significant cardiac cycle effect on pain perception, with higher pain intensity ratings, greater unpleasantness, and increased SEPs amplitudes during systole relative to diastole. This pattern suggests enhanced neural processing and subjective experience of painful stimuli coinciding with the systolic phase. These results align with growing evidence that the continuous, dynamic cortical representation of interoceptive signals, particularly cardiac afferent input, fundamentally shapes emotional experience (Azevedo, Garfinkel, et al. 2017; Gray et al. 2012) and perceptual consciousness (Al et al. 2020). Azevedo, Garfinkel, et al. (2017) proposed the amygdala response hypothesis, positing that arterial baroreceptor signals are carried by cranial nerves X (vagus) and IX (glossopharyngeal) directly to the nucleus tractus solitarius, which maintains connections with the thalamus and amygdala. Applied to the domain of pain processing, cardiac afferent input amplifies aversive stimulus processing (e.g., racial stereotyping in Azevedo's study). This pain modulation effect may be mediated by functional alterations within these neural circuits, particularly in the amygdala—a central hub already implicated in baroreceptor-mediated modulation of salient stimulus processing (Gray et al. 2009). Consistent with this pathway, extensive empirical evidence demonstrates that baroreceptor activation during cardiac systole potentiates the detection threshold and perceived intensity of negative emotional stimuli (Garfinkel et al. 2014; Tsakiris et al. 2021). As a multimodal experience, acute pain functions as an evolutionarily salient threat signal and has a protective effect on the survival of the individual, which is not only an unpleasant sensory experience but also an emotional one (Peng et al. 2019; Barnhart et al. 2019; Raja et al. 2020). Our findings, which demonstrate diastolic-phase pain attenuation compared to systolic enhancement, align with this amygdala response hypothesis. Given that pain stimuli represent evolutionarily salient threat signals and considering the amygdala's pivotal role in processing pain's cognitive-affective dimensions (Simons et al. 2014), we suggest the observed pain enhancement likely reflects these cyclic, cardiac-driven fluctuations in amygdala activity, though further neuroimaging studies will help to reveal the underlying neural dynamics.

However, several studies from Edwards' lab indicated that pain perception was reduced in systole compared to diastole (Edwards et al. 2001, 2002; Wilkinson et al. 2013), which is inconsistent with the present study. This line of Edwards' lab studies echoes the pulse inhibition hypothesis, which suggests that

baroreceptor activation during systole leads to generalized cortical inhibition (Grund et al. 2022; Motyka et al. 2019). In their studies, pain stimuli were presented at different phases of the cardiac cycle, with interoception acting independently (Edwards et al. 2001, 2002; Wilkinson et al. 2013). In contrast, the present study integrated interoceptive signals (heartbeats) with exteroceptive signals (vision), highlighting the role of this integration in pain perception. Methodological differences among the studies may help explain this discrepancy. A critical distinction between Edward et al.'s studies and the current paradigm lies in the explicit visual representation of cardiac signals. While Edwards and colleagues (Edwards et al. 2001, 2002; Wilkinson et al. 2013) examined cardiac processing under non-visualized conditions—where participants relied solely on implicit bodily awareness—our approach provided real-time cardio-visual feedback, thereby potentially enhancing metacognitive monitoring of heartbeat perception. Recent studies have manipulated the perception of interoception by providing individuals with feedback about their own heartbeats (Gong et al. 2022; Iodice et al. 2019; Solcà et al. 2018). Iodice et al. (2019) recorded participants' heartbeat signals in real-time during exercise and provided visual feedback based on these signals. Subsequently, participants were asked to estimate their level of effort during the exercise. The results showed that participants receiving visual feedback faster than their actual heartbeat exhibited exaggerated effort estimations compared to those provided with accurate visual feedback. Consistent with our findings, Gong et al. (2022) similarly reported no significant modulatory effect of BOI on pain perception using a cardiac enhanced RHI paradigm. While cardiac visualization failed to modulate BOI, it may have enhanced metacognitive awareness of cardiac signals, consequently influencing pain processing.

Recent theories conceptualize interoception in terms of predictive coding, emphasizing the predictive aspects of the processing of bodily signals and of physiological regulation. The predictive coding framework proposes that the brain continuously generates and updates predictions to interpret sensory signals—provides a mechanistic account of interoceptive processing. In this framework, the brain refines physiological control through hierarchical Bayesian inference: it issues top-down forecasts of impending interoceptive states—such as the next heartbeat—anchored in prior bodily experience. Any discrepancy between these predictions and ascending sensory evidence (e.g., a sudden painful stimulus) yields a prediction error that compels rapid updating of the internal model (Sterling 2012). Because nociceptive gain is gated by these interoceptive priors, the same error-minimizing mechanism that tunes cardiac regulation also sculpts the moment-to-moment experience of pain. Interoceptive inference involves top-down predictions (i.e., signals that a healthy body should generate) that interact with bottom-up prediction errors (i.e., mismatches between the expected and sensed interoceptive signals) (Iodice et al. 2019; Seth 2013). Our EEG findings illustrate the "inference" as well.

The current study provides further clarification regarding cardiac cycle specificity, demonstrating that interoceptive-mediated pain suppression occurs selectively during diastole. The N1 component amplitude was found to be decreased during systole, as depicted in Figure 6. The N1 component, recorded from contralateral secondary somatosensory areas, encodes the sensory-discriminative aspect of pain (Valeriani et al. 2007). The results of our SEP analysis revealed that the P2 component exhibited significantly larger amplitudes during the systolic condition compared to the diastolic condition, as depicted in Figure 6. The amplitude of the P2 component reflects pain-related activity and is related to cognition, such as attention and expectation (Jones et al. 2016; Hird et al. 2018; Ring et al. 2013). The observed enhancement of N1 and P2 during systole extends previous findings of cardiac-phase effects on pain perception (e.g., Al et al. 2020) by revealing distinct temporal windows of cardiovascular-cortical interaction. Notably, the P2 effects support the hypothesis that interoceptive signals modulate higher-order pain evaluation. Methodologically, these SEP patterns corroborate our behavioral findings while providing precise temporal markers (N1: sensory encoding; P2: cognitive evaluation) for cardiac-cycle influences on pain processing. These findings show that the interoceptive signals inhibit pain processing during diastole across both sensory and cognitive dimensions of pain (Marshall et al. 2022; Gong et al. 2022).

Our investigation into interoceptive signals was conducted using the VR-RHI paradigm, aiming to explore whether the effect of interoception on pain is influenced by the BOI. Although we successfully elicited the BOI in our study participants, it did not have a significant effect on their pain perception, as evidenced by both the lack of a significant effect in subjective reports and the objective SEPs results. Many studies have found that the BOI can produce analgesic effects (Cordier et al. 2020; Preston et al. 2020; Romano and Maravita 2014; Themelis and Newport 2018). For instance, Hegedüs et al. (2014) found that in the RHI paradigm, the experimenter brushed the participants' real and rubber hands synchronously or asynchronously, and then measured the nociceptive threshold. Their results revealed that participants' thermal pain thresholds were significantly higher under synchronous conditions compared to asynchronous conditions (Hegedüs et al. 2014). However, some studies have not found any effect of the BOI on pain perception (Gong et al. 2022; Mohan et al. 2012). The differential findings could be attributed to the material properties of body representation, such as the length and size of body parts (Martini et al. 2013, 2015). Themelis and Newport (2018) presented patients with hand osteoarthritis with a stretching illusion of the hand (the hand illusion appears longer than it actually is), then tested subjective pain ratings. The results showed that virtual stretching led to changes in body perception and a reduction in subjective pain ratings but did not affect the pressure pain threshold. In the study by Themelis and Newport (2018), participants observed a live virtual representation of their own hand, positioned in the same spatial location as their actual hand, being visually stretched simultaneously while simultaneously experiencing a corresponding sensation of their hand being stretched (visuotactile and proprioceptive signals). This manipulation altered participants' body representation, resulting in changes in pain perception. In contrast, in our experimental approach, we used the RHI combined with heartbeat-enhanced VR, which did not change the representation of the hand, and therefore no effect on pain perception was observed. However, this conclusion needs to be further validated.

This study also has some limitations. First, while our cardiac enhanced RHI paradigm provided precise interoceptive-visual

synchronization, the ecological validity of heartbeat visualization remains uncertain, as natural cardiac awareness typically occurs without such explicit external cues. Second, our findings are specifically limited to conditions with real cardiac visual feedback, leaving open how cardiac phase effects might operate in the absence of visualization or when feedback is asynchronous. The real visual feedback may have enhanced participants' interoceptive accuracy, thereby potentially confounding the relationship between cardiac signals and pain perception. Third, we did not evaluate participants' interoceptive accuracy, which may modulate pain-interoception interactions; this measurement should be incorporated in future studies. Moreover, potential confounding factors including baseline heart rate variability and anxiety levels were not systematically controlled, potentially affecting the processing of pain. Future research should address these limitations to further elucidate the interplay between interoception, body ownership, and pain perception.

In conclusion, our findings revealed that the diastolic phase is associated with attenuated pain processing, as evidenced by reduced subjective pain intensity, decreased unpleasantness, and lower N1 and P2 amplitudes in SEPs compared to the systolic phase. Notably, this interoceptive-mediated analgesia appears functionally distinct from BOI mechanisms, with BOI showing no observable influence on pain processing. These results suggest that incorporating interoceptive perception into multisensory integration could be reconciled in a predictive-coding framework, and may represent a promising avenue for developing analgesic approaches.

Author Contributions

Wenxiao Gong: conceptualization, methodology, formal analysis, funding acquisition, investigation, visualization, writing – review and editing, data curation. **Qiao Xu:** software, visualization. **Kun Liang:** data curation, project administration, investigation, validation. **Lijia Gu:** writing – review and editing. **Lihan Chen:** conceptualization, funding acquisition, formal analysis, resources, supervision, writing – review and editing.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Academic Affairs Committee of the School of Psychological and Cognitive Sciences at Peking University.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** 11-Item questionnaire for RHI and cardiac illusion. **Video S1:** Demonstration of the heartbeat-enhanced rubber hand illusion under virtual reality. This study investigated the heartbeat-enhanced rubber hand illusion within a virtual reality (VR) environment. The experiment commenced with a pre-induction proprioceptive drift (PD) assessment, where participants reported the perceived location of their actual left index finger on a virtual ruler. This was followed by a two-minute body ownership induction phase, during which the participants viewed a virtual hand in synchrony with real-time, accurate visual feedback of their own heartbeat. Following induction, participants underwent pain threshold measurements and a subsequent EEG experiment to examine the neural correlates of pain processing. They also provided subjective ratings of pain intensity and unpleasantness. Finally, a post-induction PD assessment was conducted, and the overall PD was calculated as the difference between the pre- and post-induction position estimates.