

Heartbeat-evoked cortical responses: Underlying mechanisms, functional roles, and methodological considerations

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ABSTRACT

The heart continuously and cyclically communicates with the brain. Beyond homeostatic regulation and sensing, recent neuroscience research has started to shed light on brain-heart interactions in diverse cognitive and emotional processes. In particular, neural responses to heartbeats, as measured with the so-called heartbeat-evoked potential, have been shown to be useful for investigating cortical activity processing cardiac signals. In this review, we first overview and discuss the basic properties of the HEP such as underlying physiological pathways, brain regions, and neural mechanisms. We then provide a systematic review of the mental processes associated with cortical HEP activations, notably heartbeat perception, emotional feelings, perceptual awareness, and self-consciousness, in healthy subjects and clinical populations. Finally, we discuss methodological issues regarding the experimental design and data analysis for separating genuine HEP components from physiological artifacts (e.g., cardiac field artifact, pulse artifact) or other neural activities that are not specifically associated with the heartbeat. Findings from this review suggest that when intrinsic limitations (e.g., artifacts) are carefully controlled, the HEP could provide a reliable neural measure for investigating brain-viscera interactions in diverse mental processes.

1. Introduction

Throughout life, the heart continuously and cyclically sends afferent signals to the brain. Although knowledge about neural communication between the heart and the brain is still limited, previous theories and research have proposed that interplay between visceral afferent signals and the associated cortical processing might play an important role in cognitive and emotional processes. Already Aristotle had proposed that “the seat of our sensation is the heart” (recited from [Clarke and Stannard, 1963](#)). Although we now know that such speculation is wrong, the statement still implies people's intuitive thinking that heart-related processes may play a role in cognition and emotion, a notion perpetuated by subsequent philosophers including Spinoza, Merleau-Ponty, and James. Influenced by such thinking, the field of embodied cognition suggested that bodily processes, including both sensorimotor and visceral systems, are of fundamental importance for cognition and consciousness ([Varela et al., 1991](#); [Thompson, 2007](#)), although following empirical research has been mostly focused on sensorimotor interactions ([O'Regan and NOE,](#)

[2001](#); [Legrand and Ruby, 2009](#); [Christoff et al., 2011](#)) and multisensory processing ([Blanke et al., 2015](#)). Furthermore, recent neuroscientific research is progressively targeting interoceptive processing as an important source of sensory input and proposed that cortical processing associated with internal visceral organs underlies emotional and cognitive brain processes ([Damasio, 1999, 2010](#); [Craig, 2003, 2009](#); [Critchley and Harrison, 2013](#); [Damasio and Carvalho, 2013](#); [Park and Tallon-Baudry, 2014](#)). For instance, it was proposed that continuously updated cortical maps of internal organs might be important for self-consciousness ([Damasio, 2003b, 2010](#); [Damasio and Carvalho, 2013](#)). More recently, this idea has been extended to perceptual consciousness beyond self-consciousness and emotion, and it has been proposed that cortical processing of visceral signals might underlie the subjective characteristics of perceptual conscious experiences ([Park and Tallon-Baudry, 2014](#), [Park and Blanke, 2019](#)). Although these converging ideas have suggested that visceral signals and related cortical or subcortical processing could play an important role for mental processes, notably conscious experiences including self-consciousness,

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emotion, and perceptual consciousness, these proposals remained rather speculative and lacked direct experimental support until recently.

Signals pertaining to the cortical processing of cardiac signals, the so-called heartbeat evoked potential (HEP), have filled this gap more recently. The HEP can be computed by averaging electrophysiological signals (e.g., scalp EEG, intracranial EEG, MEG) time-locked to specific peaks of simultaneously measured ECG signals (e.g., R or T waves), just like visual-evoked potentials can be obtained by averaging EEG signals time-locked to the specific timing (e.g., onset) of a visual stimulation. Although the HEP has been introduced more than 30 years ago (Schandry et al., 1986), the literature is still in its infancy and several challenges have to be met. For instance, concrete evidence of the underlying mechanisms (e.g., physiological, neural) is still missing. Most of HEP studies have analyzed and compared HEPs between experimental conditions (Park et al., 2014; Babo-Rebelo et al., 2016a; Sel et al., 2016) or groups (Pollatos and Schandry, 2004; Canales-Johnson et al., 2015; Muller et al., 2015; Schulz et al., 2015), rather than investigating the basic properties of the HEP itself, such as their neural sources and mechanisms. Furthermore, most electrophysiological researchers considered cardiac-related signals as artifacts and endeavored to remove them from other cortical signals (Viola et al., 2009). Indeed one of the most crucial intrinsic limitations of the HEP is that when using scalp EEG or MEG (but not intracranial EEG; see next section), it is heavily contaminated by ECG activity itself, as strong electrical activity generated by the heart itself can be measured on the entire body including the cortical surface. Thus, the question of whether the HEP exists and can be measured at the cortical level has remained unanswered until recently.

In spite of these limitations, researchers are increasingly employing the HEP as a neural marker reflecting cortical processing of the heartbeat or visceral processing more generally (Kern et al., 2013; Park et al., 2014, 2016, 2018; Babo-Rebelo et al., 2016a, 2016b; Sel et al., 2016). Furthermore, recent studies overcame some of the abovementioned methodological limitations, in particular by using intracranial recordings (Kern et al., 2013; Park et al., 2018). The aims of the present review are threefold. First, we overview and discuss the basic properties of the HEP (e.g., underlying physiological pathways, mechanisms, neural sources). Then we will provide a systematic review of cognitive and emotional processes the HEP has been associated with in healthy subjects and clinical patients. Lastly, we discuss methodological issues regarding the experimental design and control analyses for investigating the HEP, fostering future research on brain-visceral interactions using HEPs.

2. Basic properties of the HEP: physiological pathways, neural sources, and mechanisms

2.1. 1. physiological pathways - from the heart to brain

Brain and internal organs communicate through either neural (e.g., autonomic nervous system) or chemical mechanisms (e.g., endocrine system, immune system, circumventricular organs) (Cameron, 2009). Yet, understanding of the detailed communication pathways between the brain and the visceral organs is still incomplete. For instance, it had long been assumed that nutrient sensory input from the gut is transmitted to the brain only through hormones and not through neural pathways. However, recent research described a specific type of gut epithelial cells that activates the vagal nerve, thus revealing that gut-brain communication is also mediated via a specific neural pathway (Kaelberer et al., 2018). The precise pathways underlying the HEP are largely unknown. Based on current knowledge about the heart-brain pathways (for a review see Critchley and Harrison, 2013; Silvani et al., 2016), we here discuss several potential physiological pathways underlying the HEP (see also Tallon-Baudry et al., 2018), involving 1) baroreceptors at the aortic arch and the carotid arteries, 2) cardiac afferent neurons at the heart wall, 3) somatosensory mapping through the skin, and 4) neuro-vascular coupling in the cortex (Fig. 1).

First, it was proposed that neural signals from baroreceptors to the

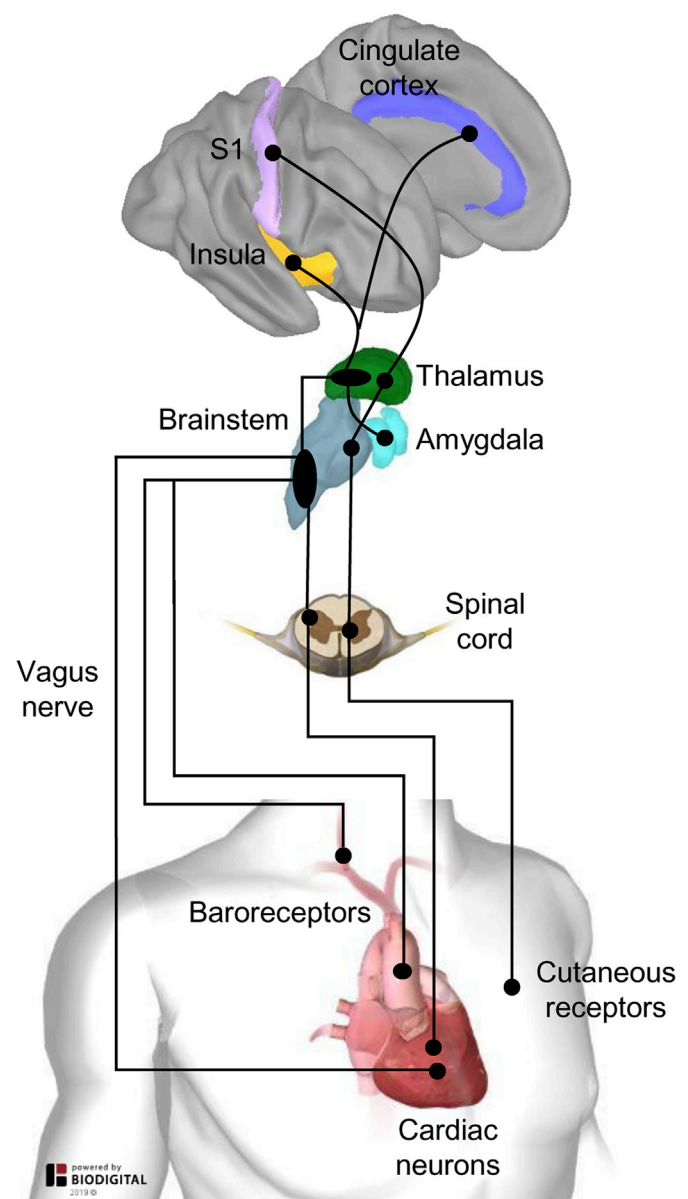


Fig. 1. Multiple physiological pathways involved in cardiac interoception and HEP generation. Cardiac afferents are projected to the cortex (e.g., the insula, cingulate cortex, amygdala, somatosensory cortex) via specific pathways starting from baroreceptors (at the aortic arch and carotid arteries), cardiac neurons (in the heart's wall), and cutaneous receptors (in the skin of the chest). Cortical and body images are generated using Brainstorm (Tadel et al., 2011) and BIODIGITAL (<https://human.biodigital.com/>), respectively.

viscero-sensory cortices are the main physiological source of the HEP (Gray et al., 2007; Garfinkel and Critchley, 2016). Baroreceptors are stretch sensors that are mainly located at the aortic arch and the carotid arteries, detecting arterial pressure changes on a beat to beat basis. Aortic and carotid baroreceptors have different sensitivity and interact with each other (Brunner et al., 1984). Increased arterial pressure (e.g., due to a rise in stroke volume or heart rate) stretches the sensory nerve endings of baroreceptors and evokes afferent neuronal firing which results in future reduction in arterial blood pressure by triggering parasympathetic vagal nerve output. Conversely, lowered arterial pressure reduces baroreceptor firing which in turn increases sympathetic nerve activity, resulting in future increases in arterial pressure (Sheehan et al., 1941). Both phasic (i.e., within a single cardiac cycle) and tonic (i.e., across several cardiac cycles) arterial pressure changes affect baroreceptor

firing, and its modulation is most sensitive to the arterial pressure changes directly above or below the baseline level, indicating the role of baroreceptor reflex is buffering arterial pressure fluctuations from the baseline (Heesch, 1999). Such afferent neural signal influx from the baroreceptors reaches the viscerosensory cortices including the insula, amygdala and cingulate cortex (Cechetto and Saper, 1987; Zhang et al., 1999), through projections to the brainstem (e.g., the nucleus of the solitary tract) and thalamus (e.g., ventromedial posterior thalamic nuclei), via the vagus nerve (for a review, see Craig, 2003; Critchley and Harrison, 2013; Garfinkel and Critchley, 2016). The HEP amplitude that appeared around 500 ms post R-peak time-window over fronto-central electrodes was shown to be associated with the cardiac stroke volume (as measured by impedance cardiography) (Schandry and Montoya, 1996), consistent with the observation that cardiac afferents from baroreceptors are centrally processed around 400–800 ms post ECG R-peak time window (Fagius and Wallin, 1980; Gray et al., 2007). However, other studies reported that the HEP modulation is not necessarily associated with changes of measured cardiac parameters themselves including peripheral blood pressure, heart rate, heart rate variability (Park et al., 2014, 2016; Babo-Rebelo et al., 2016a), that are all associated with changes in baroreceptor firing patterns.

Second, direct neural pathways between the heart and the brain might be another physiological pathway underlying the HEP generation. Cardiac afferent neurons in the wall of the heart detect both chemical and mechanical changes from the atria and ventricles and constitute both shorter and longer-latency loops involving intrinsic cardiac reflexes and central processing, respectively (Tahsili-Fahadan and Geocadin, 2017). Cardiac chemotransduction neurons generate tonic and relatively low frequency activity (e.g., around 0.1 Hz), whereas cardiac mechanotransduction neurons convey precise information regarding the mechanical cardiac status within each cardiac cycle reflecting regional muscle fascicle deformation. Cardiac neurons fire at specific phases of the ECG signal (e.g., around R or T-waves), depending on the location and transduction characteristics of the cardiac neuron. (Armour and Ardell, 2004). Thus, via direct neural pathways, which have fast conduction velocity, the HEP can be observed in relatively early time windows (e.g., shortly after R-waves, < 100 ms), as shown in animal work (Li et al., 2015). Such afferents from cardiac neurons are relayed to the nucleus of the solitary tract, through either the vagal nerve (Shepherd, 1985) or the spinal cord (e.g., the lamina I spinothalamic pathway) (Craig, 2003), suggesting that the nucleus of the solitary tract is integrating cardiac afferent signals from baroreceptors and cardiac neurons. After the nucleus of the solitary tract, cardiac afferents are projected to viscerosensory cortices via the thalamus as described above. In addition, the influence of baroreceptor and cardiac neuron on the HEP would not be mutually exclusive, as both reflect the mechanical deformation induced by heartbeat, implying their respective roles and interactions need to be further investigated.

Third, it has been shown that interoceptive signals also travel in somatosensory pathways. For instance, a patient with bilateral insular damage preserved normal cardiac awareness, whereas it disappeared when the patient's chest skin was anesthetized, suggesting the somatosensory processing conveys cardiac afferent signals (Khalsa et al., 2009). Accordingly, a recent intracranial EEG study has shown that HEPs can be recorded directly from the somatosensory cortex (Kern et al., 2013). A recent brain stimulation study further showed that transcranial magnetic stimulation (TMS) targeting the insula and somatosensory cortex impact different aspects of heartbeat sensation (Pollatos et al., 2016), although it is debatable whether TMS can specifically stimulate the insula (Zangen et al., 2005).

Fourth, other studies showed that vascular-neuro coupling occurs at the cortical level (Kim et al., 2016; O'Herron et al., 2016). It is well known that neuronal activity increases regional blood flow, which is the main principle behind functional magnetic resonance imaging. Interestingly, recent studies demonstrated that changes in blood flow also affect neighboring neuronal activity. For instance, in mice increased cerebral

blood flow diminished simultaneously recorded resting pyramidal neuronal firing rate (Kim et al., 2016), supporting the proposal that signals derived from the microcirculation can affect neuronal activity and related information processing in the brain (Moore and Cao, 2008). In addition, such dilation or contraction of blood vessels in the brain might have an artefactual influence on the HEP without changing the regional neuronal activity. However, a recent intracranial EEG study observed that the location of large blood vessels (e.g., vena anastomotica inferior) does not systematically affect the heartbeat-locked intracranial EEG signals reflecting pulse related artifacts (Kern et al., 2013).

Collectively, the reviewed data suggest that the physiological sources contributing to the HEP might be multifaceted, potentially explaining why HEP components are observed in relatively diverse cortical regions and temporal windows. However, most of these possible physiological HEP pathways have not been experimentally tested until now, likely because the measurement of detailed parameters (e.g., stroke volume, baroreceptor activity) during neuroscience experiments in humans is challenging and might require invasive methods (Winston and Rees, 2014).

2.2. Cortical sources of the HEP

Most HEP studies have been conducted using scalp EEG or MEG. HEP modulations have been reported in widely distributed sensors including frontal (Canales-Johnson et al., 2015; Babo-Rebelo et al., 2016a; Park et al., 2016; Wei et al., 2016; Gentsch et al., 2018), central (Montoya et al., 1993; Shao et al., 2011; Petzschner et al., 2019), and parietal (Babo-Rebelo et al., 2016a; Sel et al., 2016) channels. However, several factors (neural as well as methodological) may have caused such variable HEP topography. Whereas one view proposed that the insula might be the sole primary viscera sensory cortex (Craig, 2003, 2009), other evidence suggested that cortical processing of interoceptive signals is more widely distributed including, beyond the insula, cingulate cortex, amygdala, and somatosensory cortex (Kern et al., 2013; Park et al., 2018). Secondly, differences in experimental task design (applied in HEP studies) may lead to different recruitment of this network and hence different HEP topographies. Finally, number of electrodes, location of the reference electrode, and other methodological aspects vary across HEP studies, providing a further reason for the variability of HEP topography (see the next section).

More recent studies have used intracranial EEG which has greater spatial resolution (Parvizi and Kastner, 2018), and reported the neural sources of the HEP more precisely without the influence of cardiac field artifacts (Kern et al., 2013; Canales-Johnson et al., 2015; Babo-Rebelo et al., 2016b; Park et al., 2018). The first intracranial HEP study using grid electrodes reported reliable HEP activity in the somatosensory cortex during the resting state (Fig. 2a; Kern et al., 2013). However, this study did not record HEPs from viscerosensory cortex such as the insula. Other intracranial HEP research used depth electrodes, and observed HEP activity in the insula (Fig. 2b) as well as widespread cortical areas including the opercular cortex, inferior frontal gyrus, and amygdala at rest (Park et al., 2018). As shown in Fig. 2, these intracranial HEP data showed clear waveforms of phasic neural responses time-locked to the ECG R-peak with none or negligible influence of ECG artifact, providing concrete evidence that the HEP exists and can be measured at the cortex.

Although these studies provide valuable information about the cortical regions involved in HEP processing at rest, intracranial EEG has the intrinsic limitation that electrode locations cannot cover the entire cortex and are implanted for clinical purposes rather than research purposes (Parvizi and Kastner, 2018). Considering that the HEP cannot be measured using fMRI due to its slow temporal resolution, source localization methods, in particular using MEG or high-density EEG, have allowed unraveling some of the neural sources of HEP as well as its spectral characteristics. Indeed, during the last 5 years, several studies reported the result of source reconstruction either using MEG (Park and Tallon-Baudry, 2014; Babo-Rebelo et al., 2016a) or EEG

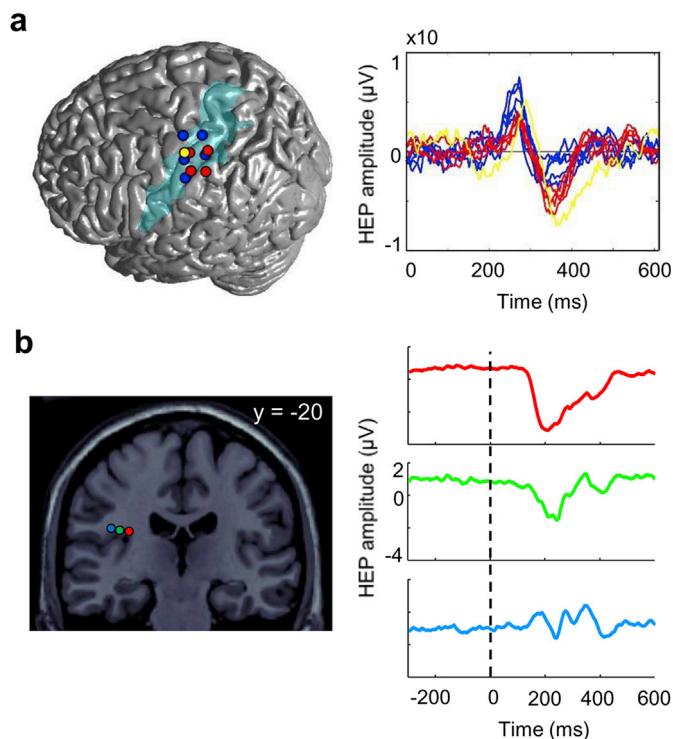


Fig. 2. Evidence of intracranial HEP at rest. Phasic neural responses time-locked to the heartbeat (i.e., HEP) was observed around 300 ms post ECG R-peak period in the somatosensory cortex (a) and insula (b), respectively using grid and depth electrodes while participants were at rest. Adapted from (Kern et al., 2013; Park et al., 2018).

(Canales-Johnson et al., 2015; Park et al., 2016) during diverse cognitive tasks (see the next section for the experimental tasks involved). As shown in Fig. 3, these studies often reported results of statistical comparison between experimental conditions, focusing differential source activations between conditions, and observed the differential HEP modulations between conditions in the viscerosensory cortices including the insula - opercular regions (Park et al., 2014, 2016; Canales-Johnson et al., 2015; Babo-Rebello et al., 2016b) and the anterior-posterior cingulate regions (Park et al., 2014, 2016; Babo-Rebello et al., 2016a) as well as the inferior parietal lobe (Park et al., 2014). Although both MEG and scalp EEG source signals are contaminated by ECG artifacts, accompanied ECG results showing no difference between conditions suggest that these source level results reflect neural activity responding to heartbeats, rather than ECG signals itself. Interestingly, some of these regions, notably the ventral anterior cingulate cortex - ventromedial prefrontal cortex (Park

et al., 2014; Babo-Rebello et al., 2016a), and posterior cingulate cortex - precuneus (Babo-Rebello et al., 2016a; Park et al., 2016), overlap with the so-called default mode network (DMN) that spontaneously fluctuates at rest (Fox and Raichle, 2007). Accordingly, another line of research has shown that visceral signals including heart rate (Wong et al., 2007), respiration (Tort et al., 2018), stomach motility (Rebollo et al., 2018) could be an important source of fluctuations of ongoing cortical activity within the DMN. Taken together, these findings support the previous proposal that neural responses to heartbeats, as measured by the HEP, impact diverse cognitive functions through modulating the ongoing neural activity in the DMN (Park et al., 2014; Park and Tallon-Baudry, 2014; Winston and Rees, 2014; Babo-Rebello et al., 2016a).

2.3. Mechanisms underlying HEP generation in the cortex

How is the HEP generated in the cortex? In general, two different mechanisms have been shown to generate event-related potentials (ERPs) evoked by diverse sensory inputs such as visual- and auditory stimuli (Makeig et al., 2002; Mazaheri and Jensen, 2006; Sauseng et al., 2007; Lopour et al., 2013): the additive evoked potential and phase-reset model. According to the additive evoked potential model, ERPs are generated by adding stimulus-evoked responses in single trials, whereas the phase reset model proposes that ERPs are generated by resetting of phases of ongoing neural activities.

Time-frequency decomposition analysis, in both phase (e.g., inter-trial coherence, ITC; measuring coherence of phases across single trials) and amplitude (e.g., spectral power measuring amplitude modulation) domain (Tallon-Baudry et al., 1996), can help distinguish between both ERP models (Sauseng et al., 2007). For instance, the phase resetting mechanism predicts that HEP will be accompanied by increased ITC without changes in power, whereas the additive evoked potential mechanism predicts that heartbeats will induce increased power, regardless of ITC changes (see Fig. 4a; Shah et al., 2004; Sauseng et al., 2007). A recent intracranial EEG study has applied such analysis to HEPs (Park et al., 2018), and observed that the HEP is accompanied by increased ITC (around 200 ms after the ECG R-peak, in 4–10 Hz) without changes in spectral power, thus supporting the phase resetting model underlies the HEP generation (Fig. 4b). In other words, this finding suggests that at each heartbeat the phase of ongoing neural activity is re-aligned regarding the timing of the heartbeat onset. Furthermore, this finding, that HEP is associated with the phase modulation rather than amplitude, provides robust evidence that the HEP does not reflect a mechanical artefactual effect such as the dilation of blood vessels, as such mechanical artifact would likely induce changes in the amplitude rather than phase of EEG signals (Luck, 2014).

To summarize, although most recent HEP research, in particular using intracranial recordings, is beginning to shed light on the neural sources and mechanisms underlying the HEP, our understanding of the

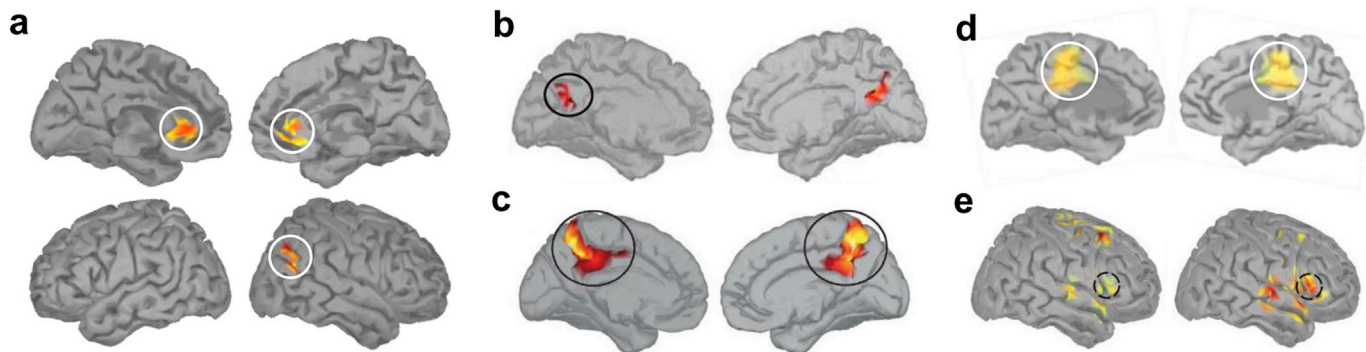


Fig. 3. Neural sources of the HEP. Source localization analysis identified neural sources of HEP during diverse cognitive tasks in the ventral anterior cingulate cortex, ventromedial prefrontal cortex, inferior parietal lobe (a), precuneus (b, c), mid-posterior cingulate cortex (d), beyond the insula-operculum regions (e). Adapted from (Park et al., 2014, 2016; Canales-Johnson et al., 2015; Babo-Rebello et al., 2016a, 2019).

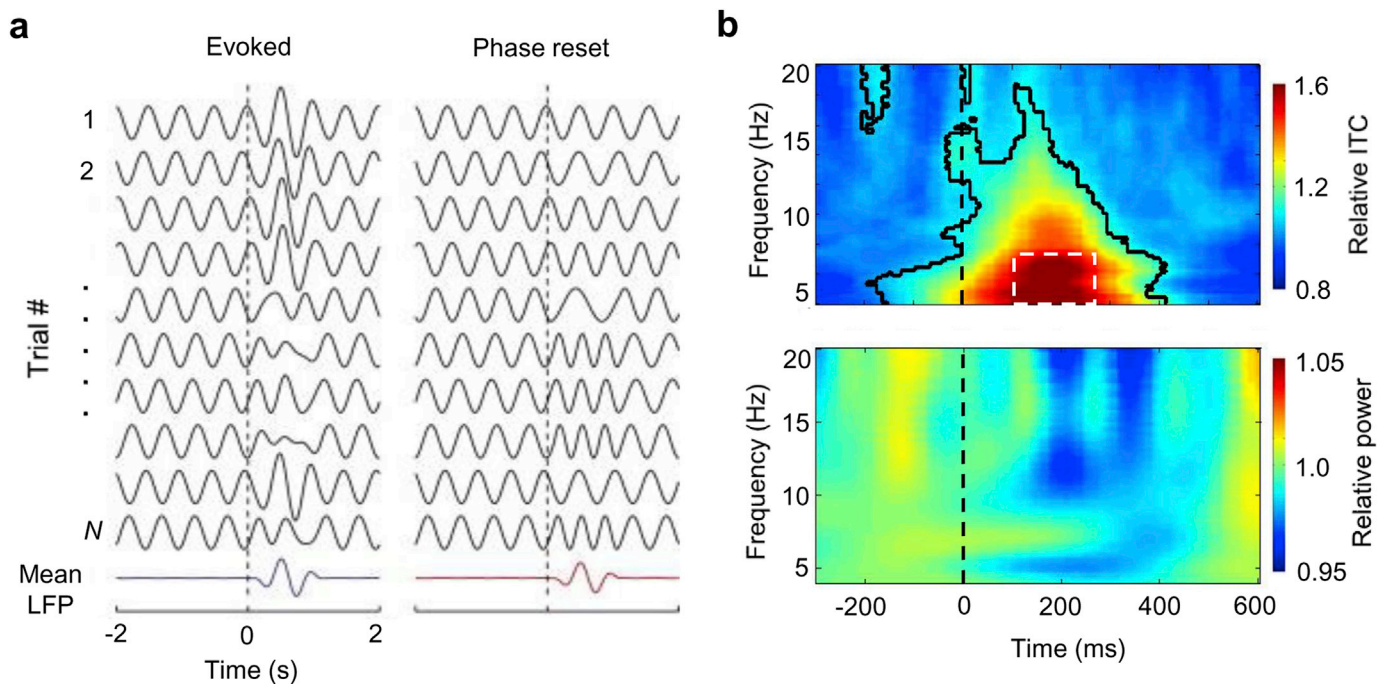


Fig. 4. Phase-reset mechanism underlies HEP generation at the cortex. (a) When averaging several single trial electrophysiology data, two differential mechanisms (i.e., evoked or phase-reset) can underlie the generation of event-related potentials. Adapted from (Lopour et al., 2013). (b) HEP was accompanied by increased phase concentration across trials without changes in power, suggesting phase-reset mechanism underlies the generation of HEP. Adapted from (Park et al., 2018).

fundamental properties of HEP is still limited. Future research, potentially using animal models combined with invasive techniques, including single-unit recordings and pharmacological intervention (see Li et al., 2015) would be needed to further unravel the fundamental properties of HEP.

3. Functional roles of the HEP in mental processes

3.1. Heartbeat sensation

The majority of HEP research has investigated whether neural responses to heartbeats, as measured by the HEP, are associated with mental processes, including heartbeat sensation, emotional feelings, perceptual awareness, and self-consciousness. Early HEP studies focused on the role of the HEP in heartbeat sensation (Schandry et al., 1986; Schandry and Weitkunat, 1990; Montoya et al., 1993; Schandry and Montoya, 1996; Pollatos and Schandry, 2004; Pollatos et al., 2005). Most of these HEP studies applied the heartbeat counting task (Schandry, 1981; Garfinkel et al., 2015), although different tasks have been also used to measure participants' heartbeat sensation (for a systematic comparison of different tasks, see Petzschner et al., 2019). In the heartbeat counting task, participants are instructed to count and report the number of heartbeats during the predefined time intervals without taking their pulse: the heartbeat perception score is computed based on the comparison between counted and recorded numbers of heartbeats.

Schandry and colleagues, who developed the heartbeat counting task (Schandry, 1981), were also the first to report the HEP (Schandry et al., 1986). Based on the observation that people vary in the heartbeat counting task, the authors investigated the HEP as a neural correlate of a detectable sensory input signal during the heartbeat counting task. They repeatedly observed that participants with higher heartbeat counting score (e.g., >0.85, for the criterion see Pollatos and Schandry, 2004) show a larger positive HEP amplitude modulation which appeared around 200–400 ms post R-peak time-window over fronto-central electrodes, compared to the participants with lower heartbeat counting scores (Montoya et al., 1993; Schandry and Montoya, 1996; Pollatos and

Schandry, 2004). Such HEP modulations during the heartbeat counting task were also enhanced after heartbeat sensation training (Schandry and Weitkunat, 1990) and positively correlated with behavioral performance (Pollatos and Schandry, 2004). Whereas most of these previous studies reported differential HEP amplitudes between different groups of participants, segregated based on the heartbeat counting score, a recent study further showed that the HEP is also associated with the focus of attention (e.g., interoceptive or exteroceptive) manipulated in the same participants (Petzschner et al., 2019). In addition, a recent study reported that such HEP modulations related to heartbeat sensation can be observed even in 5-month-old infants (Maister et al., 2017).

Of note, recently the validity of heartbeat counting task has been criticized (for a review, see Brener and Ring, 2016), as this measure has been shown to be associated with non-sensory top-down processes (Ring et al., 2015), and participants' bias (e.g., underestimation of heartbeats), making the heartbeat counting score problematic (Zamariola et al., 2018). Thus, although links between the HEP amplitude and the heartbeat counting score have been repeatedly observed, development of a task properly measuring heartbeat sensation ability, potentially by applying advanced psychophysical methodology (Brener and Ring, 2016), would be beneficial for better understanding the role of the HEP in heartbeat sensation (Khalsa et al., 2018; Petzschner et al., 2019).

3.2. Emotional feelings

Subsequent studies used the HEP as a cortical marker of cardiac processing or visceral processing more generally, and investigated its potential role in other mental processes, beyond heartbeat sensation. Since William James's influential proposal that "emotion is the feeling of bodily changes" (James, 1890), interoceptive processing, in particular the heart, has been associated with the emotional process. Following up research which has shown that peripheral cardiac parameters (e.g., heart rate, heart rate variability, ECG amplitude) are associated with emotional states (for a review, see Kreibitz, 2010), other studies used the HEP (rather than cardiac parameters themselves) to investigate the potential link between emotional process and cardiac-related cortical processing.

The HEP amplitude around 250 ms post ECG R-peak time window over frontal electrodes was more negative while participants were making affective judgments for visual faces compared to control judgments (Fukushima et al., 2011). Another study showed that pain, which accompanies unpleasant emotional experiences, was associated with the HEP amplitude modulation (Shao et al., 2011). In this study, when the participants experienced coldness-induced unpleasant pain, a more negative HEP amplitude was observed in the 200–600 ms post ECG R-peak latency range over the fronto-central regions, compared to the control condition, and this HEP modulation correlated with measured subjective pain intensity and unpleasantness ratings. Another study showed that higher arousal (induced by continuously presenting emotional stimuli) is associated with more positive HEP amplitude over parietal electrodes compared to that of lower arousal mood states (Luft and Bhattacharya, 2015). Other studies reported that emotional valence induced by either pictures (Kim et al., 2019) or movie clips (Couto et al., 2015) was associated with negative HEP amplitude modulations over the fronto-central electrodes, and such emotion-related HEP modulations were suppressed when the content of emotional stimulation was expected compared to when it was unexpected (Marshall et al., 2017; Gentsch et al., 2018).

Several reviewed studies (Fukushima et al., 2011; Luft and Bhattacharya, 2015; Marshall et al., 2017) further analyzed the associated cardiac parameters including the heart rate, heart rate variability, and ECG amplitude, but no difference was observed between experimental conditions which HEP differences were found (but see, Luft and Bhattacharya, 2015). Bearing in mind the possibility that these studies might have failed to capture the subtle changes in cardiac parameters, we suggest that the HEP provides a sensitive cortical index of cardiac processing reflecting emotional and arousal state changes, which are not necessarily associated with changes in cardiac parameters themselves. In addition, previous research showed that different phases of the cardiac cycle (e.g., at systole or diastole) impact emotional judgement, which was accompanied by neural activity changes in the periaqueductal gray matter (Gray et al., 2012) and amygdala (Garfinkel et al., 2014). Future research should investigate how peripheral cardiac signals (e.g., cardiac phase) interplay with the HEP, and how they respectively contribute to emotional feelings.

Furthermore, a few clinical studies showed that mental disorders involved in emotional dysfunction, such as depression and nightmare disorder, are associated with abnormal HEP modulations. The HEP amplitude as measured by the global field power (Lehmann and Skrandies, 1980) in a group of patients with major depression, recorded during a heartbeat counting task, was lower compared to healthy controls

(Terhaar et al., 2012). Another recent study analyzed the HEP in nightmare disorder patients which are characterized by strong negative emotions and found that the nightmare patient group showed more positive HEP amplitude compared to controls, specifically during REM sleep, which correlated with the patients' mood score (Perogamvros et al., 2019), suggesting the HEP reflects abnormal emotional state during REM sleep in the nightmare patients.

3.3. Perceptual awareness and self-consciousness

Beyond emotional processing, it has been speculated for a long time that such brain-visceral interaction might play an important role in conscious experiences, including perceptual awareness (Park et al., 2014; Park and Tallon-Baudry, 2014; Salomon et al., 2016, 2018) and self-consciousness (Damasio, 1999; Craig, 2009; Critchley and Harrison, 2013). To experimentally test the link between brain-heart interactions and perceptual awareness, Park and colleagues combined HEP analysis with a visual detection paradigm and hypothesized that the amplitude of HEP or heartbeat evoked response (HER, for MEG data) before the stimulus onset might be able to predict participants' visual detection performance (Park et al., 2014). The authors observed that the amplitude of the HER localized in the ventral anterior cingulate cortex, ventromedial prefrontal cortex and inferior parietal lobe (Fig. 3a) during the prestimulus interval significantly correlated with the hit rate of the visual detection task (Fig. 5), supporting the hypothesis that brain-visceral interaction plays an important role in perceptual awareness (Park and Tallon-Baudry, 2014).

With respect to self-consciousness, it has been proposed that interoceptive signals and their neural processing are of fundamental importance for self-consciousness (Damasio, 1999; Craig, 2009; Critchley and Harrison, 2013). For instance, Damasio pointed out that the cortical mapping of the interoceptive signal is continuous and relatively invariant, very much as we experience self-consciousness (Damasio, 1999, 2003b), and proposed that continuously updated maps of the internal state of the body enable self-consciousness (Damasio, 1999; Damasio, 2003b, a; Damasio, 2010; Damasio and Carvalho, 2013). Accordingly, recent studies used the HEP to investigate the potential link between self-consciousness and brain-visceral interactions. By combining HEP analysis with the full-body illusion (FBI) paradigm which experimentally induces changes of (bodily) self-consciousness (Lenggenhager et al., 2007; Blanke and Metzinger, 2009; Blanke, 2012; Blanke et al., 2015; Park and Blanke, 2019), the HEP amplitude around 300 ms after the ECG R-peak over fronto-central regions was shown to covary with the experimentally modulated self-identification changes (Fig. 6a; Park et al.,

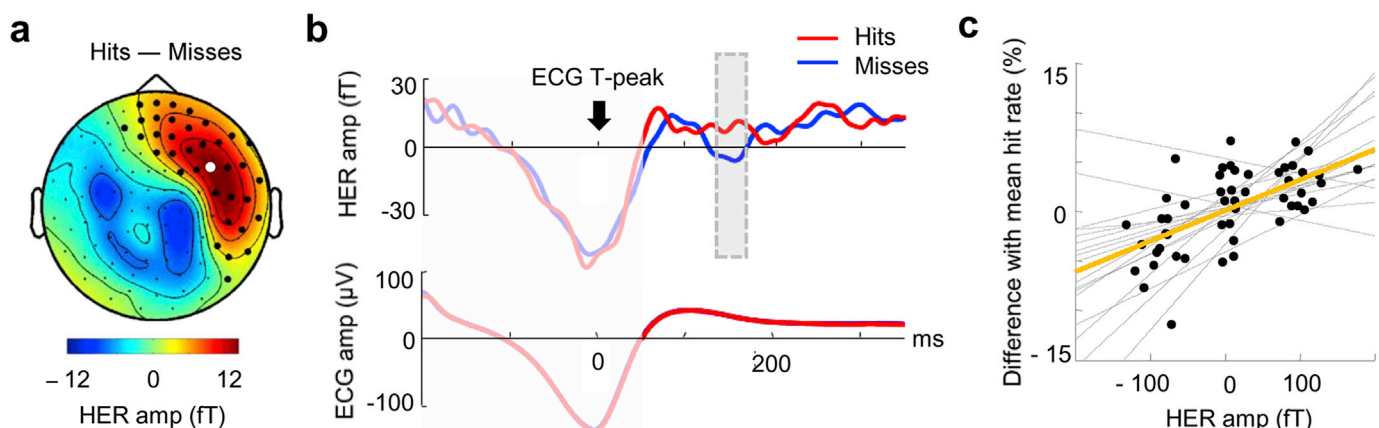


Fig. 5. Prestimulus HER amplitude predicted visual detection performance. While performing a visual detection task, between hit and miss trials, differential prestimulus HER amplitudes were observed in the fronto-central sensors (a) around 150 ms after the ECG T-wave, without accompanying ECG amplitude differences (b). (c) Mean HER amplitudes within the significant cluster significantly correlated with behavioral visual detection performance (i.e., hit rate). Adapted from (Park et al., 2014).

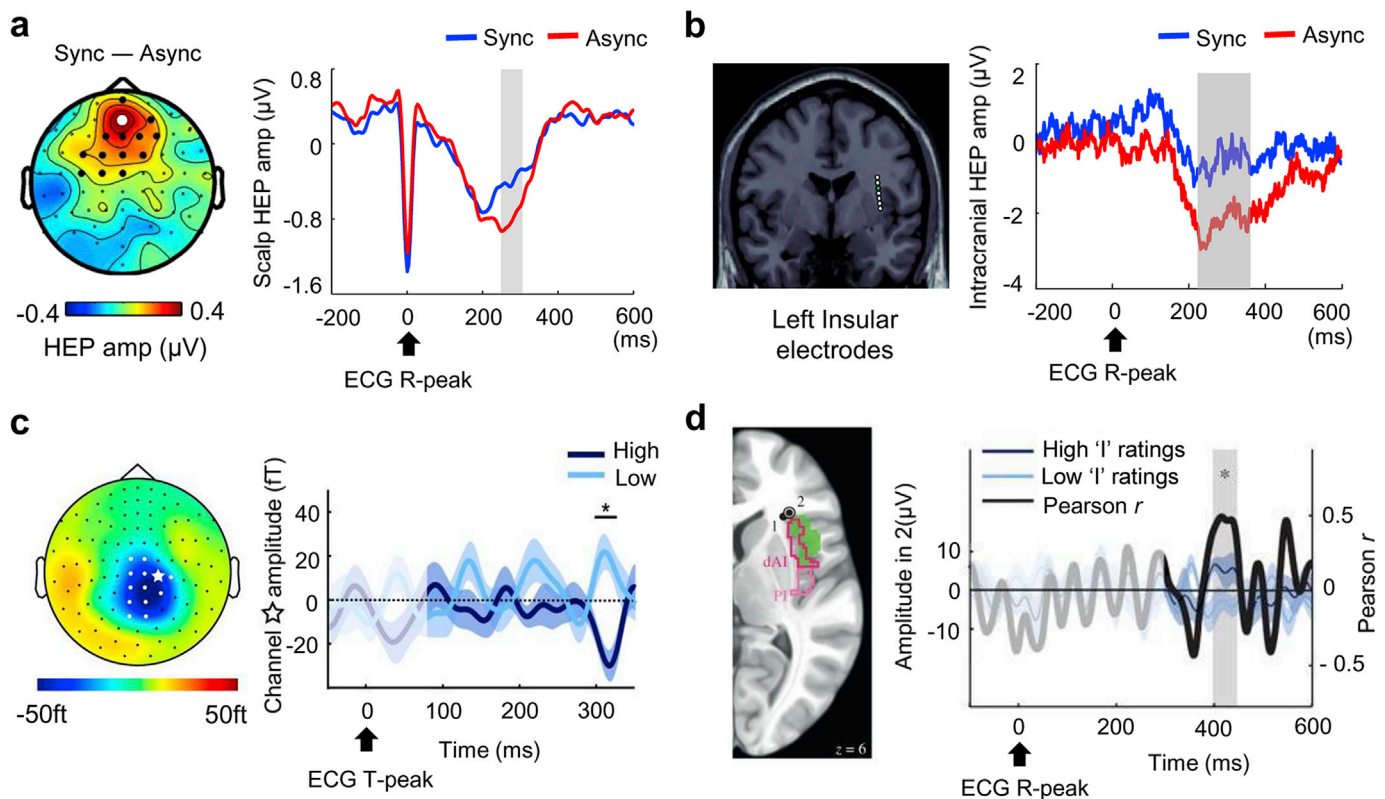


Fig. 6. Self-related HEPs. (a) The HEP amplitude was associated with changes in the self-identification scores which were experimentally induced using synchronous or asynchronous visuo-tactile stimuli. Comparable results were obtained using intracranial EEG data which were recorded in the insula (b). Adapted from (Park et al., 2016, 2018). (c) HER amplitudes were associated with the degree of self-relatedness during a spontaneous thought fluctuations. Comparable results were obtained using intracranial EEG data which were recorded in the insula (d). Adapted from (Babo-Rebelo et al., 2016a, 2016b).

2016). In the same study, source localization analysis identified the posterior cingulate and insula as sources of observed self-related HEP effects (Fig. 3d). A follow-up intracranial HEP study used the same FBI paradigm and confirmed that self-related HEP can be recorded in the insula (Fig. 6b; Park et al., 2018), with negligible influence of ECG artifact. Another EEG study further confirmed that illusory face ownership is associated with the HEP amplitude modulation in the 200–300 ms post ECG R-peak time window recorded at the right parieto-central sensors (Sel et al., 2016). Furthermore, using MEG recordings, Babo-Rebelo and colleague demonstrated a link between the HER and cognitive aspect of self-consciousness using an experimental paradigm that measured the degree of self-relatedness in participants' spontaneous thought flow while they were freely mind-wandering (Babo-Rebelo et al., 2016a). In the study, the authors compared the HER between 'high self' and 'low self' trials and showed the amplitude of HER in the precuneus and ventromedial prefrontal cortex (Fig. 3b) reflected the measured self-relatedness (Fig. 6c). A follow-up intracranial EEG study using the same paradigm confirmed that the HEP amplitude in the insula is indeed associated with the degree of measured self-relatedness (Fig. 6d; Babo-Rebelo et al., 2016b). A recent study further showed that differential HER changes in similar regions (e.g., precuneus, mid-posterior cingulate regions; Fig. 3c) were found when participants were imagining either themselves (from a first-person perspective) or familiar others (from a third-person perspective) (Babo-Rebelo et al., 2019).

Other studies examined the role of the HEP in mental disorders associated with atypical states of self-consciousness and personality traits such as depersonalization (Schulz et al., 2015) and borderline personality disorder (Muller et al., 2015). For instance, it has been proposed that the core feature of depersonalization is a feeling of disembodiment which can be considered as an impairment of self-consciousness (Medford, 2012). A study reported that healthy controls showed a more negative

HEP amplitude during the heartbeat counting task compared to the resting state condition over the fronto-central electrodes around 500 ms after the R-peak, whereas patients with depersonalization did not show such HEP differences between conditions (Schulz et al., 2015). Patients with a borderline personality disorder, which commonly share overlapped symptomatology with depersonalization patients (Hedrick and Berlin, 2012), showed more positive HEP amplitude over central regions in the 400–600 ms post R-peak time window during the resting state condition, compared to healthy controls (Muller et al., 2015). Although these results are in accordance with the proposed link between the HEP and self-consciousness, follow-up studies are needed to confirm the specific role of HEP in self-related mental disorders such as schizophrenia (Shaqiri et al., 2018) and heautoscopy (Heydrich and Blanke, 2013).

To summarize, earlier HEP research observed a close relationship between conscious heartbeat sensation and the HEP modulation, whereas more recent research has investigated the role of HEP in mental processes, notably associated with emotional feelings and self-consciousness, thus providing empirical evidence for theoretical proposals highlighting the role of brain-visceral interactions in emotion and self-consciousness. Indeed it has been proposed that interoception, emotional feelings, and self-consciousness are closely related to each other and commonly associated with visceral processing (Damasio, 2003a; Critchley et al., 2004). 'Interoceptive predictive coding' has recently proposed that emotional feelings and aspects of self-consciousness depend on the active inference of interoceptive afferent signals (Seth, 2013; Seth and Critchley, 2013; Barrett and Simmons, 2015; Ainley et al., 2016; Allen et al., 2016; Petzschner et al., 2017; Allen and Friston, 2018; Owens et al., 2018). Future empirical research needs to validate, though, whether the HEP reflects interoceptive predictions or prediction errors (see also Petzschner et al., 2019), and empirically test the interoceptive prediction model using the HEP.

4. Methodological issues – separating artefactual effects from the HEP

As a complete discussion on the methodology of HEP analysis is beyond the scope of the present review, we here focus on the one important methodological issue: how to separate artefactual effect from the genuine HEP signal? In general, in HEP studies, it is critical to show that the observed HEP modulation does not result from physiological noises or other EEG components that are not specifically associated with the heartbeat.

4.1. Heartbeat-related physiological artifacts

Physiological noises that are time-locked to the heartbeat, such as cardiac field artifact (Dirlich et al., 1997) and pulse artifact (Kern et al., 2013) can confound the HEP. For instance, when using scalp EEG or MEG, typical HEP waveforms reflect a mixture of neural activity time-locked to the heartbeat and cardiac field artifact (Fig. 5; 6) because such strong electrical activity generated by the heart itself can be recorded at the scalp. Thus, several methods have been proposed to at least partially remove such physiological noises from the HEP. For instance, a few HEP studies applied diverse methods such as simple subtraction method (Montoya et al., 1993), principal component analysis (Schandry et al., 1986; Pollatos et al., 2005), and independent component analysis (ICA; Terhaar et al., 2012; Park et al., 2014). Although these methods have been shown to be effective in removing prominent artefactual components from the HEP, they cannot completely separate all artefactual components from the HEP, as can be shown in the ICA corrected HEP results (Park et al., 2014). In addition, such correction methods may remove genuine HEP components as well. Other studies applied non-computational approaches by restricting the time of interest for the HEP analysis to the period that is known to be less affected by the cardiac field artifact (Dirlich et al., 1997; Gray et al., 2007; Park et al., 2014). For instance, during the time period from the decay of ECG T-wave to the beginning of the next R-wave, the cardiac field artifact measured on the scalp decreases to the less than 1% compared to the ECG amplitude measured at the chest, and it has been suggested that this time period might be considered as (almost) free from cardiac field artifact for the HEP research (Dirlich et al., 1997). Furthermore, when a study involves two different experimental conditions or groups, as most reviewed HEP studies, comparison of ECG signals between conditions could be critical to show that observed HEP effects do not result from the different ECG activity. Thus, if one finds a differential HEP amplitude, but not in the simultaneously recorded ECG amplitude between two experimental conditions, one can safely infer that such differential HEP reflects genuine neural activity time-locked to the heartbeat. Of note, considering none of these methods provides a complete way for controlling cardiac field artifacts, it would be preferable to use some of these methods together in a complementary way. For instance, if one observes different HEP modulations, without accompanying ECG difference, between experimental conditions consistently using both non-corrected and corrected data, this may suggest that the observed HEP effect is not associated with the cardiac field artifact or artifact-correction method applied. On the contrary, it would be problematic if one does not report the result of ECG comparison between conditions or groups, solely based on the assumption of the artifact-free time window (Muller et al., 2015).

On the other hand, when using intracranial EEG, it has been shown that pulse related artifacts are the main confound of the intracranial HEP (Kern et al., 2013; Park et al., 2018), whereas the cardiac field artifact has negligible influence. A recent intracranial HEP study showed that time-frequency analysis could be useful for excluding pulse artifacts from genuine intracranial HEP, based on the fact that pulse artifacts are characterized by stereotypical oscillatory pattern lower than 2 Hz (Park et al., 2018). Although never reported to date, single-unit recordings might be able to provide artifact-free neural responses to heartbeats.

4.2. Non-cardiac related cortical activity

Neural activities that are not evoked by the heartbeat can still confound the HEP if they occur simultaneously. Thus, when specific exteroceptive sensory stimuli (e.g., visual stimuli) or behavior (e.g., button presses) are time-locked to the cardiac signals due to experimental design, one needs to be careful about dissociating the HEP from neural activities evoked by other sensory stimuli or behavior. In such experimental designs (Canales-Johnson et al., 2015; Sel et al., 2016), although carefully controlled using additional statistical procedures by the authors, EEG activities time-locked to the heartbeat could be confounded by visual or motor-evoked cortical potentials merely due to their temporal overlaps, suggesting that the delay between heartbeat and other sensory stimuli need to be considered while designing a HEP experiment. Furthermore, even if sensory or motor activities are not time-locked to the heartbeat, it is critical to show that observed EEG activity that is time-locked to the heartbeat is indeed specifically associated with cardiac processing, rather than some other background EEG activity. To formally check this possibility, a control analysis using surrogate R-peaks has been applied (Park et al., 2014, 2016; Babo-Rebelo et al., 2016a). In brief, when some HEP effect is observed, one can apply the very same HEP analysis repeatedly (e.g., >100 times) using a surrogate or fake ECG R-peaks, which can be generated by randomly shifting the original R-peaks. Then, if the original HEP effect is observed only when using the real R-peaks, but not the surrogate R-peaks, it would strongly suggest that the original HEP effect is specifically associated with cardiac processing. In other words, this control analysis would show that by time-locking EEG signal to the ECG onset, one can gain additional information specifically associated with the cardiac processing.

In this last section, we discussed methodological considerations specifically associated with potential artefactual sources of the HEP. It's worth briefly mentioning other methodological limitations and concerns regarding HEP analysis. In particular, the reviewed data showed that HEP modulations have been observed in relatively distributed sensors (e.g., frontal, central, parietal) and time windows (e.g., 200–600 ms after the ECG R-peak). Although such HEP variability might at least partially come from genuine physiological properties (e.g., different physiological pathways and neural sources) and different experimental paradigms, it may also stem from lack of standardized methods for HEP analysis. The latter should include 1) use of standardized reference electrode selection (e.g., the common average, linked earlobes, or tip of the nose), 2) automatized and standardized control analyses for excluding the influence of cardiac field artifact (e.g., avoid selecting components based on visual inspection when applying ICA), 3) standardized baseline selection (e.g., no baseline correction or using specific pre R-peak time window), 4) justification for selecting regions and times of interest for HEP analysis. Sharing of standardized and automatized analysis pipelines (for both sensor and source level analysis) across researchers, would be beneficial for reducing the potential sources of such variability, thus making the results from different HEP studies more comparable each other.

5. Conclusion and future directions

It is evident that the brain does not exist independently of the visceral organs, and there is growing interest in how interactions between the brain and internal organs, in particular the heart, contribute to mental processes beyond homeostatic regulations. The reviewed data suggest that the HEP measuring neural responses to cardiac signals may involve multiple physiological pathways (e.g., baroreceptors, afferent cardiac neurons, somatosensory mapping through the skin, neuro-vascular coupling at the cortex) and neural structures (e.g., the insula, anterior-posterior cingulate cortex, amygdala, somatosensory cortex), implying its multifaceted nature. Of note, none of the discussed physiological pathways underlying the HEP have been confirmed by basic neuroscience research in animals. On the other hand, the reviewed data on

functional roles of the HEP in mental processes suggest that the HEP associates with particular aspects of conscious experiences such as perceptual awareness, self-consciousness, and emotional feelings, thus providing empirical evidence supporting long-standing theoretical proposals on the role of brain-viscera interactions in consciousness. We further discussed that careful consideration of the experimental design and data analysis are needed to dissociate physiological noises or non-cardiac related cortical processing from the genuine HEP components. In addition, considering that most HEP research has employed relatively simple data analysis of the evoked cortical responses, future research using more advanced data analysis techniques including network level connectivity and causality analyses are needed to further unravel the detailed cortical mechanisms of the HEP. Finally, future research should investigate cortical responses associated with other diverse visceral organs including the gut, stomach, and lungs (see Adler et al., 2014; Richter et al., 2017; Allard et al., 2017; Rebollo et al., 2018; Tort et al., 2018), and how they are integrated with exteroceptive sensory signals (Park and Blanke, 2019), and their potential roles in diverse mental processes.

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