NEURAL-HEART INTERACTIONS IN THE HEALTHY AND INJURED BRAIN

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A thesis submitted to the University of Birmingham for the degree of
DOCTOR OF PHILOSOPHY

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September 2021

ABSTRACT

Introduction

Integrating internal and external signals is fundamental for perceiving and interacting with the world via the body. In particular, interoceptive predictive coding frameworks describe these integrated mechanisms as vital for embodied selfhood, emotional experience, and a unified first-person perspective. By definition, a disorder of consciousness patient has dysfunctional awareness of their self and their environment. Despite the dual diagnostic criteria, research has focused almost exclusively on external perceptual awareness, leaving internal self-related aspects of awareness largely unexplored. Thus, we sought to detect neural markers of self-related interoceptive processing with the aim that their detection may predict the recovery of self-awareness in acute unresponsive disorders of consciousness.

Experiment one

First, we aimed to identify neural markers of interoceptive (i.e., cardiac) and exteroceptive (i.e., auditory) integration in healthy individuals. We presented sequences of sounds at a short delay (i.e., perceived synchronous) or long delay (i.e., perceived asynchronous) from the heartbeat, with half the trials including an omission. We analysed heart-evoked potentials (i.e., HEPs) during omissions to measure pure predictive mechanisms without contaminating auditory responses. Pre-omission HEP responses differed across short delay and long delay trials, potentially reflecting differences in heartbeat-driven expectations of sounds. Furthermore, attending to internal heartbeat sensations modulated omission-evoked responses, supporting the role of attentional-precision in regulating cross-modal predictive mechanisms (i.e., state precision). However, we did not observe modulation of HEP/omission-evoked responses by individual difference in interoceptive ability, which doesn't support the proposed regulating role of trait precision in predictive coding frameworks. Therefore, HEP mechanisms of interoceptive and exteroceptive integration operate partially under interoceptive predictive coding. However, we observed inconsistent evidence of modulation by precision-weighting.

Experiment two

Second, we sought to determine whether the lack of observed trait precision modulation (i.e., by interoceptive ability) and, therefore, inconsistency with precision-weighting resulted from individual differences in the perceived timing of heartbeat sensations. Thus, in experiment two, we tailored the perceived synchronous cardio-audio delays to each individual to test the influence of trait precision more sensitively. Despite this, we observed no significant modulation of HEPs by state or trait precision. Nonetheless, we replicated the robust HEP effect indicative of cardio-audio expectation. Thus, overall, our findings are inconsistent with a precision-weighted predictive coding view. However, it could be that participants relied less on attentional/state precision under a more individually-tailored task. Furthermore, assessing interoceptive ability is challenging, and thus, our interoceptive performance measures may not accurately reflect trait precision.

Experiment three

Finally, cortical processing of heartbeats at rest is thought to index self-related aspects of awareness, such as embodied selfhood and the formation of a first-person perspective. Hence, we investigated the prognostic potential of resting HEPs and cardiac measures in acute unresponsive patients. We observed no convincing evidence of HEPs or cardiac measures predicting recovery from acute unresponsiveness, three or six months post-assessment. This lack of evidence suggests resting HEPs are not useful for consciousness prognoses. However, greater prognostic value may be found in HEPs during high-level self-processing or interoceptive-exteroceptive integration (i.e., Experiments one and two).

Discussion

In summary, we observed robust HEP evidence of interoceptive signals guiding expectations of exteroceptive stimuli. However, we observed inconsistent evidence of modulation of HEPs by state precision and no evidence of modulation by trait precision. Thus, we need more explicit definitions of the manipulation and measurement of precision in predictive coding frameworks to test their influence on interoceptive predictive mechanisms accurately. Finally, although previous evidence indicated the diagnostic value of HEPs, we observed no convincing evidence of their prognostic potential. It is possible that during rest, self-cognitive mechanisms reflected in HEPs are reduced. Therefore, investigating HEPs during tasks involving high-level self-processing or interoceptive-exteroceptive integration may be more valuable for awareness prognoses.

ACKNOWLEDGEMENTS

I would like to express my appreciation to all of those who supported me during my PhD journey. It's been a wild trip, but I wouldn't change it for the world. First, I am incredibly grateful for the constant support and guidance from my supervisor Damian Cruse over the five years, starting from when I was only a masters student. I have learned an infinite amount of knowledge from his intelligence, and I appreciate that he never stopped encouraging or challenging me. It is a shared opinion from everyone whose been a member of his lab: that he is a leader, not just a boss. Importantly, I'd also like to thank Howard Bowman and Sarah Garfinkel for their valuable feedback while assessing my thesis.

I am especially thankful that I was lucky enough to be a member of the BEST lab in the world: with genius support from Rodi (La Jefa) no matter how annoying I was, for the repetitive tears of laughter with Consu: my bumper car chair buddy from the office, my hubby Seansy: also my official PA for the duration of my PhD, Sara: my reliable gig and weird events buddy, Davinia for hints and intellectual tips with all my presentations, as well as so many unforgettable memories with Davide, Ruth, Roya, and Mel. Furthermore, I will never forget the colourful and loud office members of 111, including extended memberships to Seb (wigs in all), Al, and Tom. May the welcomed distraction and pisco shots continue forever.

It goes without saying the infinite appreciation I have for my family during the completion of my PhD. My mum, as always, has been an endless source of emotional support, with extra help from her communications with 'mother earth'. My sister Flee, who visited me the most out of everyone: you always restored my happiness and energy, and of course, Little Lily for your undeniable hilariousness and equal adorableness. Moreover, I am abundantly grateful for Gabbino, who constantly supported me during my insanity and did all he could to make sure I would climb the PhD mountain—not forgetting cuddles from my floofs: Max and Podd.

I could always rely on the support from my coven: Serena and Mary (special thanks for our hikes and adventures), as well as, Pete: my study buddy until the end, Lucille who I could vent to about anything, and Ben for inspirational (and sometimes head hurting) metaphors, and our extended motley crew. Additionally, I thank my best friend Alanna for our phone calls from across the ocean and Honnor for being the best fairy godmother ever.

Finally, I am exceptionally appreciative of the Medical Research Council's funding. They have supported my growth as a researcher tremendously, and fundamentally, the research in this thesis would not exist without them. Most importantly, I am thankful to all the patients, family members, and participants who contributed to this research, I will always be impressed by their selfless willingness to contribute towards science.

LIST OF PUBLICATIONS

Below includes a list of the published and pre-printed work in this thesis and indicates the author contributions for each:

1. Banellis, L., & Cruse, D. (2020). Skipping a beat: heartbeat-evoked potentials reflect predictions during interoceptive-exteroceptive integration. *Cerebral Cortex Communications*, *1*(1), tgaa060. https://doi.org/10.1093/texcom/tgaa060

Author contributions: LB and DC designed the experiment, LB collected and analysed the data, LB and DC interpreted the results and contributed to the final manuscript.

The above publication represents the body of work in CHAPTER 2, as it is published.

2. Banellis, L., & Cruse, D. (2021). Heartbeat-evoked potentials during interoceptive-exteroceptive integration are not consistent with precision-weighting. *bioRxiv*. https://doi.org/10.1101/2021.02.03.429610

Author contributions: LB and DC designed the experiment, LB collected and analysed the data, LB and DC interpreted the results and contributed to the final manuscript.

The above preprint represents the body of work in CHAPTER 3, as it is published.

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KEY ABBREVIATIONS

(P)DOC	(Prolonged) Disorder of Consciousness
VS/UWS	Vegetative State/Unresponsive Wakefulness Syndrome
(e)MCS	(Emergence from) Minimally Conscious State
CMD	Cognitive Motor Disorder
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale Extended
CRS-R	Coma Recovery Scale-Revised
EEG	Electroencephalography
ECG	Electrocardiography
fMRI	Functional Magnetic Resonance Imaging
HEP	Heart-Evoked Potential
ERP	Evoked-Response Potential
AEP	Auditory-Evoked Potential
SSEP	Somatosensory-Evoked Potential
TBI	Traumatic Brain Injury
CT	Computer Tomography
AIC	Anterior Insular Cortex
ACC	Anterior Cingulate Cortex
CFA	Cardiac Field Artefact
HRV	Heart Rate Variability
IBI	Inter-Beat Interval
BPQ	Body Perception Questionnaire
VNS	Vagus Nerve Stimulation
EPIC	Embodied Predictive Interoceptive Coding

CHAPTER 1: INTRODUCTION TO PROGNOSIS IN DISORDERS OF CONSCIOUSNESS AND THE VALUE OF NEURAL SIGNATURES OF INTEROCEPTION

1.1 Overview and Research Questions

Determining the state of awareness in unresponsive patients is a challenge of modern medicine, with critical implications for rehabilitation assignments or life-support decisions (Young et al., 2021). Current clinical standards focus exclusively on assessing patients' awareness of the environment, leaving a crucial aspect of the consciousness diagnostic criteria unassessed: **self-awareness**. A wealth of evidence demonstrates the importance of internal bodily signals (i.e., interoception) for embodied selfhood, emotional experience, and a unified first-person perspective. Thus, interoception provides a means of investigating self-cognition in unresponsive patients (Azzalini et al., 2019; Craig, 2009; Critchley & Garfinkel, 2018; Tsakiris & Critchley, 2016). In particular, the functional integration of internal and external stimuli in the brain (i.e., interoceptive-exteroceptive integration) is essential for experiencing and interacting with the world via the body as an embodied self (Seth & Friston, 2016). Thus, in this thesis, we first characterise heart-evoked potential (HEP) signatures of interoceptive-exteroceptive integration and investigate whether these integrated mechanisms operate under a predictive coding framework. Importantly, we determine if high-level variations in precision (i.e., attention and individual differences in interoceptive perception) modulate cross-modal integrated mechanisms. Furthermore, HEPs at rest provide valuable self-cognitive information, and thus, finally, we explore the prognostic utility of resting HEPs in predicting recovery from acute unresponsive states. Therefore, the overarching aim of this research is to investigate the functional significance of HEPs during interoceptive-exteroceptive integration and rest, subsequently exploring their prognostic potential in acute unresponsive patients.

Chapter 1 introduces the literature that inspired this thesis. First, I present the challenge of researching the elusive phenomenon of consciousness and explain the clinical difficulty of assessing awareness recovery from unresponsive states. Second, I introduce the value of interoception for investigating internal self-related aspects of awareness. Third, I present an interoceptive predictive coding account of self-cognition. Finally, I highlight heart-evoked potentials as a marker of interoceptive processing and conclude with an experimental thesis outline.

1.2 The Problem of Consciousness

Consciousness is a constellation concept with complex and multifaceted dimensions. It is the most familiar yet perplexing phenomenon of Cognitive Neuroscience, with all of us accustomed to the individual *what it is like* to have a unique subjective experience (otherwise known as qualia) (Lewis, 1956; Nagel, 1974). This familiarity is coupled with the recollection of distinct nothingness or unconsciousness when we awaken from dreamless sleep or anaesthesia. There is a long-standing explanatory gap in understanding how the material electrical firing of neurons gives rise to abstract conscious experience (Levine, 1983). The difficulty in bridging this gap (i.e., discovering a complete mechanistic explanation of subjective experience) is known as the classic mind-body problem or hard problem of consciousness, distinguished from easy solvable problems such as perception and memory (Chalmers, 1995; Crane & Patterson, 2012). However, the existence of a problem or even consciousness itself is a matter of intense debate, with some arguing the pursuit to bridge the objective and subjective is an illusion created from category mistakes (Pigliucci, 2013).

Not only is there considerable discussion concerning the definition of consciousness with respect to other cognitive processes, but also with classifying dimensions of consciousness itself. Block (1995) distinguished phenomenal consciousness from access consciousness. The former represents the whole private experience (i.e., the redness of red or the warming sensation from the sun). The latter reflects only the content available for use in thought, speech, and action. Hence, Block suggests that our rich phenomenal experience is not restricted to the limited set of representations we access and can report to others (Block, 1995). Another major division of consciousness is of its levels and contents (i.e., wakefulness and awareness). Wakefulness describes the level of arousal, such as being asleep or awake. While, awareness depicts the subjective content of an individual's experience (encompassing both access and phenomenal consciousness) (Plum & Posner, 1983). For this thesis, we focus on the contents of awareness and their recovery from unresponsive states.

1.3 Disorders of Consciousness

Divisions of conscious experience are beneficial when defining disordered consciousness after severe brain injury. For example, both wakefulness and awareness dimensions of consciousness are dysfunctional when comatose, the initial and most degraded disorder of consciousness (DOC). Comatose patients lack a normal sleep-wake cycle and cannot be awakened by painful, auditory, or visual stimulation. Thus, comatose is formally defined as absent wakefulness and absent awareness (Royal College of Physicians, 2020). This acute unresponsive phase lasts formally between six hours and four weeks and initially includes a period of sedation. Once sedation is removed, the trajectory varies from death to the recovery of consciousness, with some patients remaining in the grey zone of prolonged disorders of consciousness (PDOC) (Owen, 2017; Rosenfeld et al., 2012). PDOC conditions include vegetative state (also known as unresponsive wakefulness syndrome (VS/UWS)) and minimally conscious state (MCS). VS/UWS is the most severe PDOC condition, characterised by an intact sleep-wake cycle and reflexive/spontaneous behaviours, but no behavioural indication of self or environmental awareness (i.e., wakeful but absent awareness) (Childs et al., 1993). In contrast, MCS patients demonstrate inconsistent but reproducible behavioural evidence of awareness, and the level of behavioural responsiveness distinguishes patients into MCS- or MCS+ (i.e., wakeful with minimal awareness). For example, MCS- patients demonstrate simple responses such as purposeful visual tracking or localising motor reactions. In contrast, MCS+ patients exhibit higher-level responses such as following motor commands or intentional communication. Finally, emergence from MCS (eMCS) is defined as the recovery of reliable and consistent high-level behavioural reactions, such as functional interactive communication or functional use of objects (Royal College of Physicians, 2020). Only once DOC symptoms have persisted for more than four weeks can an official PDOC diagnosis of VS/UWS or MCS be given. Thus, patients transitioning from comatose to VS/UWS before four weeks may not be formally diagnosed as VS/UWS but are instead broadly defined as acutely unresponsive (see Figure 1).

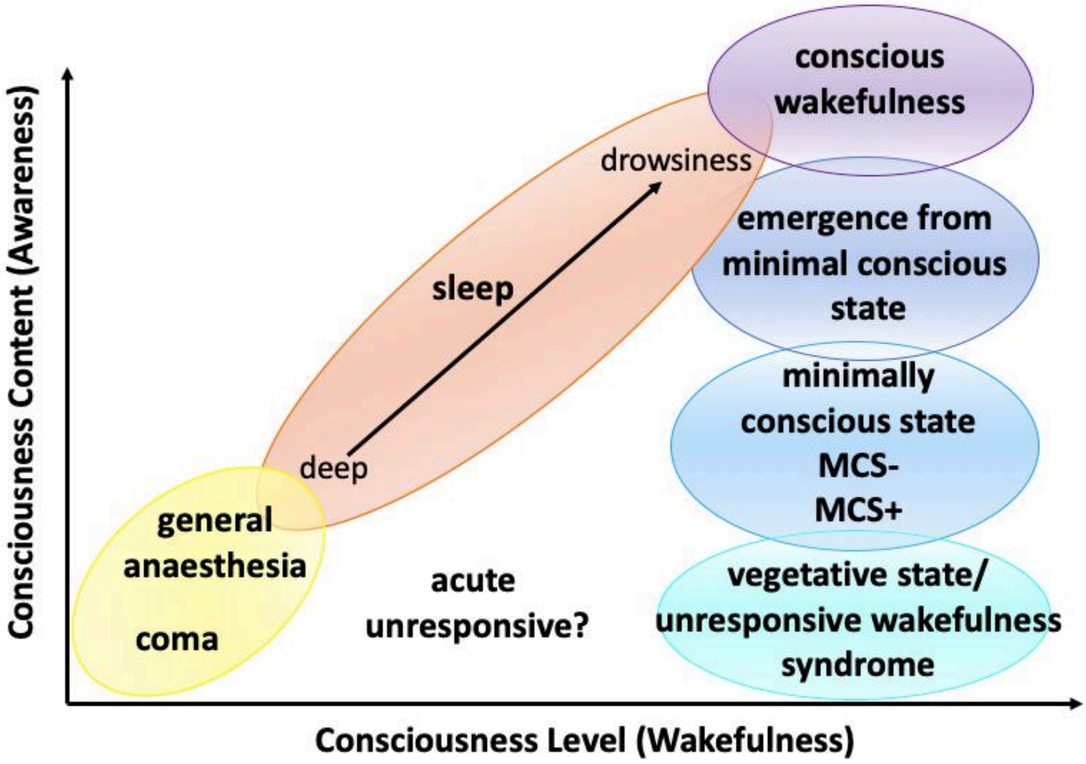

Figure 1. *Simplified representation of the two major dimensions of consciousness: levels (i.e., wakefulness) and contents (i.e., awareness) (Plum & Posner, 1983). Those in coma and under general anaesthesia lack awareness and wakefulness, while patients with vegetative state/unresponsive wakefulness (VS/UWS) syndrome are wakeful but lack awareness. Patients in a minimally conscious state (MCS) are wakeful and demonstrate minimal/fluctuating evidence of awareness such as visual tracking (MCS-) or command following (MCS+), whereas patients who are emerging from MCS recover high-level communicative responses. Healthy variation in consciousness contents and levels occur during sleep (orange) to conscious wakefulness (purple). The position of acute unresponsive patients in this diagram is uncertain as they may recover some level of wakefulness and awareness, but they may not be able to demonstrate behavioural evidence (as cognitive motor dissociation patients). Furthermore, a VS/UWS diagnosis is not given until unresponsive symptoms have persisted for 4 weeks. Thus, the diagnosis of awareness in these acute unresponsive patients is in limbo until this point (Figure adapted from Jöhr et al., 2015).*

Current clinical standards of evaluating awareness in acute brain injured patients include neurological, pupillary, and behavioural assessments. The Glasgow Coma Scale (GCS) is commonly used to behaviourally assess acute levels of consciousness by evaluating eye, verbal, and motor responses (Marmarou et al., 2007; Teasdale & Jennett, 1974). Although widely used, the GCS doesn’t consider brainstem reflexes or neurological assessments, which are substantial contributing factors when evaluating consciousness state. Furthermore, often patients are intubated, which prevents evaluation using the verbal subscale completely. Wijdicks et al (2005) developed the Full Outline of UnResponsiveness (FOUR) scale to accommodate the GCS shortcomings by assessing brainstem reflexes (i.e., pupil and corneal reflexes), respiratory patterns, as well as eye and motor responses (Foo et al., 2019; Wijdicks et al., 2005). In addition to the behavioural and pupillary assessments, clinicians conduct neurological examinations, including reflex responses to noxious stimulation (Edlow et al., 2021). These assessments are useful for gauging conscious state in acute critical care settings; however, they do not differentiate between prolonged VS/UWS or MCS diagnoses. Clinicians employ more comprehensive repetitive behavioural assessments for PDOC diagnoses, such as via the JFK Coma Recovery Scale-Revised (CRS-R), the Wessex Head Injury Matrix (WHIM), or Secondary Modality Assessment and Rehabilitation Techniques (SMART) (Giacino et al., 2004; Gill-Thwaites & Munday, 2009; Royal College of Physicians, 2020; Shiel et al., 2000).

Although behavioural assessment is the current clinical standard, motor, visual or auditory impairment and fluctuations in vigilance limit possible behavioural responses, resulting in high misdiagnosis rates in PDOC patients once re-assessed by experienced teams (Andrews, 1996; Childs et al., 1993; Schnakers, Vanhaudenhuyse, et al., 2009a). For example, Schnakers et al (2009a) found that 41% (18/44) of patients diagnosed as VS/UWS by clinical team consensus were determined MCS once re-evaluated using the CRS-R. Furthermore, 89% (16/18) of patients with an uncertain diagnosis were defined as MCS once re-evaluated, and 10% (4/41) of patients diagnoses as MCS were reconsidered as eMCS (Schnakers, Vanhaudenhuyse, et al., 2009a). Moreover, Childs et al (1993) observed a misdiagnosis rate of 37% (18/49) in VS/UWS/comatose patients. Andrews et al (1996) detected a 43% misdiagnosis rate (17/40) in VS/UWS patients, seven of whom were previously considered VS/UWS for more than a year and three for over four years. More recent evidence emphasises the importance of repetitive behavioural assessments (Wang et al., 2020). Specifically, the misdiagnosis rate of VS/UWS patients was much higher (38.2% (34/89)) with multiple CRS-R assessments than a single reassessment (24.7% (22/89)), as compared to previous clinical consensus. These multiple assessments reclassified 16.7% (8/48) of eMCS patients previously diagnosed as MCS (Wang et al., 2020). Furthermore, when re-evaluating patients over 13 weeks, both VS/UWS and MCS patients were more likely to be reclassified in the morning than the afternoon (Cortese et al., 2015). Thus, behavioural diagnosis varies considerably, highlighting high misdiagnosis rates are still present today (Wang et al., 2020).

Even when PDOC patients are assessed repetitively and over large timescales by trained clinicians using the 'gold-standard' (CRS-R) behavioural approach, misdiagnosis persists in patients who cannot behaviourally respond due to dysfunctional motor capabilities. Indeed, a myriad of neuroimaging research highlighting the presence of residual cognitive abilities in behaviourally non-responsive patients (Cruse et al., 2011; Gosseries et al., 2016; Owen et al., 2006). This began with a ground-breaking study that demonstrated covert cognition in a patient behaviourally diagnosed as VS/UWS (Owen et al., 2006). Owen et al (2006) used functional magnetic resonance imaging (fMRI) and an intelligent mental imagery paradigm to demonstrate residual cognition in behaviourally unresponsive patients. The task involved imagining playing tennis or imagining navigating around their house. This revealed supplementary motor area activation during tennis imagery and parahippocampal gyrus, posterior parietal-lobe, and lateral premotor cortex activation during navigation imagination. The patients' brain activation was indistinguishable from healthy controls, demonstrating complex cognitive capabilities despite presenting no behavioural evidence (Owen et al., 2006). Moreover, Monti et al (2010) replicated the detection of covert cognition in a further four patients (17% out of 24). Notably, one of the four was able to communicate yes or no answers to simple questions by performing this mental imagery paradigm, demonstrating the potential for communication via brain imaging in behaviourally unresponsive patients (Monti et al., 2010).

Although this research crucially revealed residual cognitive abilities in patients thought to be unconscious, fMRI is an expensive technique that not all patients can access. Furthermore, an MRI scan is impossible for some patients with metal implants or severe injury that impedes transference to a scanner. Thus, Cruse et al (2011) used a cheaper, portable method of electroencephalography (EEG) to detect residual cognitive abilities at the bedside via a motor imagery paradigm. He found that three patients (19% of 16) modulated their EEG activity by following motor imagery commands of imagining moving their right hand or toes, with a classifier accuracy of approximately 70%. Specifically, similar to healthy controls, patients demonstrated a reduction in power of mu (7-13Hz) and beta (13-30Hz) over the lateral premotor cortex for imaged hand movements and lateral premotor cortex for imagined toe movements (as well as an increased power of these frequency bands over contralateral premotor regions) (Cruse et al., 2011). Thus, covert cognition has been demonstrated in patients using various neuroimaging techniques, including those implemented at the bedside.

This line of innovative research resulted in a new class of PDOC defined as Cognitive Motor Dissociation (CMD) (Schiff, 2015). CMD patients have the cognitive capacity to access consciousness but have dysfunctional motor ability, which prevents behavioural reporting of their experience. Thus, CMD may be considered a motor disorder rather than a disorder of consciousness, as they exhibit access consciousness via neuroimaging (Block, 1995). Fernández-Espejo et al (2015) observed a mechanistic explanation of covert awareness in the absence of intentional movement (i.e., CMD) by analysing the preservation of the central thalamic mesocircuit through dynamic causal modelling and fibre tractography. In healthy controls, physical motor execution (i.e., moving the right hand to hit a ball) revealed excitatory coupling between the thalamus and primary motor cortex, in contrast to the same imagined movement. Crucially, the connecting fibres between these regions were disrupted in a CMD patient, but these connections were intact in a control patient capable of motor execution. Thus, this revealed the importance of motor thalamocortical projections for motor execution and that damaged motor thalamocortical fibres might represent a signature of CMD (Fernández-Espejo et al., 2015). These findings are analogous to the mesocircuit hypothesis of disordered consciousness, describing damage in the anterior forebrain mesocircuit (i.e., prefrontal/frontal-striatopallidal-thalamocortical system) as a central mechanism of DOC (Schiff, 2010). In particular, this mesocircuit model describes metabolic suppression of the central thalamus as causing regulatory disruption in frontoparietal systems in DOC patients. Specifically, this model describes VS patients as resulting from damage in the central thalamus and its projections, and CMD from damage in the ventrolateral thalamus and associated connections (Fernández-Espejo et al., 2015; Schiff, 2010, 2015). A meta-analysis revealed a 14% prevalence of CMD in 563 chronic patients diagnosed with VS/UWS who demonstrated covert neurological command following in previous fMRI and EEG studies (Kondziella et al., 2016).

Although less research has been conducted on the prevalence of CMD in acute unresponsive patients, Claassen et al (2019) revealed a similar percentage (15%) in 104 acute brain injured patients in the intensive care unit, via an EEG motor command paradigm (i.e., commands to open/close their right hand). Importantly, these acute brain-injured patients with CMD had a higher likelihood of functional recovery after one year (Claassen et al., 2019). Thus, detecting early evidence of covert cognition in acute unresponsive patients is especially important for enhancing the chance of recovery. Prognoses of awareness or functional recovery are extremely valuable as they can guide critical care decisions regarding rehabilitation assignment or life-sustaining treatment decisions. Early prognoses of awareness are essential as there is a critical window of opportunity (i.e., golden hour or silver day after injury) in which acute brain-injured patients are most responsive to medical interventions. Furthermore, previously, this window of opportunity extended to legal decisions in which there was a time limit for decisions regarding the withdrawal of life-sustaining treatment (Kitzinger & Kitzinger, 2013). Although, since 2018, it is no longer mandatory to seek judicial approval for the withdrawal of feeding tubes in DOC patients, accurate early prognoses can facilitate critical decisions that significantly impact the quality of life of patients and family members of severely injured patients (Kitzinger & Kitzinger, 2020). Moreover, prognoses in DOC are significant for clinical centres with limited resources to facilitate the accurate allocation of resources to patients most likely to recover. Crucially, DOC patients exhibit a considerable economic weight, with an estimated cost of £5.8bn a year in the UK and $76.5bn in the US, encompassing rehabilitation costs, social services, and lost earnings from family caregivers (Formby et al., 2015; Peterson et al., 2021). Thus, accurate early prognoses of awareness from acute unresponsive states are fundamental for allocating expensive health resources and ensuring clinicians ethically fulfil patients' best interests.

1.4 Prognostic Markers of Recovery from DOC

Prognostic neuroimaging research, such as via electroencephalography (EEG), has assisted with detecting neural prognostic markers regarding the recovery of awareness. For example, identifying early sensory evoked responses demonstrates the preservation of low-level sensory processing pathways, such as somatosensory evoked potentials (SSEPs) or brainstem auditory potentials within 30ms of stimulation. Specifically, bipolar transcutaneous electrical stimulation of the median nerve at the wrist produces multiple SSEP components: at the plexus (N9), cervical spinal cord (N13), brainstem (P14), and contralateral primary somatosensory cortex (N20 in posterior central sulcus, P25 and N35 in peri-central cortex) (Allison et al., 1991). Observing these SSEP components highlights the transmission of somatosensory information from the periphery to the cortex and thus, demonstrates the functioning of different levels of somatosensory processing (Chiappa & Ropper, 1982; Comanducci et al., 2020). For example, the absence of bilateral N20 components reflects dysfunction of the transmission of somatosensory information from the median nerve to the cortex, and thus, is a strong predictor of poor outcome (i.e., reflecting VS/UWS or death) with 100% prognostic specificity (Fischer et al., 2006; Goldie et al., 1981; Logi et al., 2003). Essentially, if the processing of low-level sensory information is damaged, the brain will not support high-level cognitive functions dependent on these sensory systems. These early sensory responses are thought to demonstrate the 'receiving state' of sensory systems but do not necessarily reflect the 'sending state' of the network from the cortex (Comanducci et al., 2020). Despite this, Cruse et al (2014) indicated that the amplitude of later SSEP components (i.e., N20, P25 and N35) predicted the recovery of awareness and functional outcome (as measured by the Glasgow Outcome Scale), although accuracy at the single-patient level was only 46% (Cruse, Norton, et al., 2014).

Long-latency (100ms+) event-related potentials (ERPs) demonstrate the preservation of neural pathways involved in more complex cognitive processes. Therefore, long-latency ERPs have the potential to predict favourable outcomes by detecting the preservation of cognitive processes essential for functional recovery (i.e., a marker of attention demonstrates the patient can attend to instructions from other people) (Lew et al., 2006). The novelty oddball paradigm involves presenting repetitive auditory standards with deviant stimuli (consisting of a different latency, pitch, or duration) interspersed and having novel sounds such as the subject's name infrequently presented (Holeckova et al., 2006). This paradigm provides electrophysiological information regarding several cognitive processes. For example, early responses to each tone

(N1) demonstrate intact auditory sensory processing. Responses to deviant tones (Mismatch Negativity (MMN)) highlight automatic sensory memory processes. Finally, reactions to rare salient stimuli (novelty P3/P3a) demonstrate involuntary attention-enhancing cognitive functions (Morlet & Fischer, 2014). MMN and P3a have been observed during sleep, while anaesthetised and in response to subliminal stimuli, suggesting responses are pre-attentive and not dependent on conscious awareness (Atienza et al., 1997; Azabou, Rohaut, et al., 2018; Bernat et al., 2001; Brázdil et al., 2001; Heinke et al., 2004; Koelsch et al., 2006). Despite this, unconsciousness substantially reduces P3 amplitudes in comparison to larger conscious P3 components reflecting the breakthrough of stimuli into the fringe of conscious awareness (Bowman et al., 2015; Harris et al., 2021; Shirazibeheshti et al., 2018). Furthermore, the presence of an MMN response has successfully predicted awakening from coma (i.e., recovery of wakefulness defined as opening eyes), with a high specificity of 93% and sensitivity of 53% (Fischer et al., 2004, 2006; Kane et al., 1993, 1996; Morlet & Fischer, 2014; Naccache et al., 2005). A recent study with deeply sedated patients found that MMN amplitude was significantly larger in those with eye-opening within 28 days (Azabou, Rohaut, et al., 2018). Compatible with the MMN research, the presence of a novelty P3a component elicited by the subjects name is highly correlated with awakening at three months after coma, with 85% specificity (Fischer et al., 2008). Overall, the MMN and P3 prognostic research suggest that long-latency ERPs demonstrate the functional state of multiple cortical pathways and, thus, the potential to recover subsequent cognitive processes. Although both MMN and P3a responses are associated with the recovery of wakefulness, these responses do not necessarily predict awareness recovery. This is because MMN and P3a responses are pre-attentive and not dependent on conscious awareness, thus, they reflect processing that is necessary but not sufficient for consciousness. Therefore, neural signatures may need to reflect higher-level cognitive processes to provide prognostic information regarding awareness with high accuracy.

Bekinschtein et al (2009) expanded the standard oddball paradigm to include local and global auditory violations in pitch. This revealed auditory regularity processing of different levels: a local P3a and global P3b response. Lower-level local violations produced responses not dependent on attention, including an initial MMN response at ~130ms, followed by a P3a response of 200-300ms, whereas global violations produced a P3b response ~260-700ms, only elicited when participants were attentive and aware of the global violation rule (Bekinschtein et al., 2009). Thus, as the global P3b response is dependent on attention and awareness, it may reflect a marker of conscious processing. Notably, the global effect was only observed in MCS patients, contrary to unaware VS/UWS patients, supporting the global P3b as a neural signature of conscious processing. In addition to being diagnostically valuable, the global P3b response provides prognostic promise by predicting behavioural consciousness recovery in intensive care non-communicating patients with high specificity (84%) and high positive predictive value (80%), but low sensitivity (35%) (Perez et al., 2021). Finally, detecting EEG markers of high-level language comprehension is another valuable method of predicting awareness recovery (Gui et al., 2020; Sokoliuk et al., 2020). For example, Sokoliuk et al (2020) recorded EEG in acute unresponsive patients while presenting streams of isochronous monosyllabic words, which built phrases and sentences. Inter-trial phase coherence was computed to demonstrate patients with EEG responses synchronised to the rhythm of phrase and sentence presentation, and thus, highlight those with intact high-level speech comprehension capabilities. Cortical tracking of phrases and sentences significantly correlated with outcome from acute unresponsiveness (measured via the Glasgow Outcome Scale Extended). Notably, this improved the accuracy of prognosis than behavioural measures alone (Sokoliuk et al., 2020). Therefore, neural markers of high-level cognitive processes such as speech comprehension and global attention-dependent pattern recognition provide prognostic value of the recovery of awareness.

In summary, a range of EEG markers has provided prognostic value in DOC patients. Early somatosensory and brainstem auditory potentials demonstrate the preservation of sensory pathways, which reflect the receiving of low-level sensory information (Chiappa & Ropper, 1982; Comanducci et al., 2020). Thus, the lack of early sensory responses within 30ms of stimulation has strong predictive specificity for poor outcome, and the amplitude of later SSEP components predict favourable outcomes (Fischer et al., 2006; Goldie et al., 1981; Logi et al., 2003). In contrast, long-latency ERPs provide evidence of the integrity of pathways involved in more complex cognitive processes, such as the MMN and P3a/P3b responses (Bekinschtein et al., 2009; Morlet & Fischer, 2014). Thus, the MMN response, which reflects automatic sensory memory processes, and the P3a, representing attention enhancement, predicts awakening from coma with high specificity (Fischer et al., 2008; Naccache et al., 2005). Higher-level attention and awareness-dependent P3b potentials and markers of language comprehension are predictive of the recovery of overt behavioural evidence of consciousness (Perez et al., 2021; Sokoliuk et al., 2020).

1.5 Internal awareness via interoception

To date, prognostic research has focused exclusively on detecting neural responses to external stimuli. Some consider external responses to describe the functional state of only a subset of consciousness neuronal networks responsible for external-perceptual awareness. However, clinicians define DOC as dysfunctional awareness of the self and the environment (Royal College of Physicians, 2020). Thus, internal self-related aspects of awareness need to be characterised to ensure the prognosis of awareness as a whole. Indeed, Demertzi et al (2011) proposed awareness is distinguished into internal and external components which arise from distinct networks. The external/extrinsic network comprises lateral fronto-temporo-parietal cortices, reflecting perceptual awareness of sensations from the external world (i.e., vision, audition, external somatosensations, olfaction, and gustation). While, the internal/intrinsic network encompasses midline anterior cingulate, mesiofrontal, posterior cingulate, and precuneal cortices, representing stimulus-independent awareness of self-related cognition, memories, and emotions (Demertzi et al., 2013). Interestingly, intensity ratings of spontaneous internal and external thoughts were anticorrelated in 80% of participants (24/31) (Vanhaudenhuyse et al., 2011). Specifically, on average, awareness switched between internal and external modes every 20 seconds, although the prompting frequency (i.e., also 19/20 seconds on average) may bias this estimation. The awareness ratings corresponded to activity in associated networks: internal awareness intensity ratings correlated with activity in medial brain areas (i.e., internal/intrinsic system), and external awareness intensity ratings associated with activity in lateral fronto-parietal regions (i.e., external/extrinsic system) (Vanhaudenhuyse et al., 2011). Thus, activity in the networks supporting internal and external awareness was anticorrelated, along with the behavioural ratings.

Healthy neurologically switching of activity in internal and external networks is thought to contribute towards conscious cognition. In support, the internal and external networks are functionally disconnected in patients without awareness (i.e., VS/UWS patients) (Demertzi et al., 2013). Furthermore, MCS patients demonstrate partial recovery of the external network but metabolic dysfunction of the internal network and thalamus (Thibaut et al., 2012). Moreover, recovery of metabolic activity in intrinsic and extrinsic networks (and the thalamus) correlated with consciousness CRS-R scores, including patients in VS/UWS, MCS, eMCS, and locked-in syndrome (LIS) (Thibaut et al., 2012). Therefore, these studies highlight the importance of characterising both internal and external awareness for consciousness recovery. Despite this, current clinical standards focus solely on detecting awareness of the environment, leaving internal self-related aspects of awareness largely unexplored.

Interoception is the perception of visceral bodily sensations such as heartbeat contractions or the expansion of lungs, including feelings concerning the body's internal state such as hunger or nausea (Cameron, 2001; Sherrington, 1952). In contrast, exteroception refers to the perception of stimuli outside the body (i.e., vision, audition, tactile), and proprioception signifies the perceived location and movement of the body. A wealth of data has demonstrated interoception's role in numerous high-level cognitive processes, including internal self-related aspects of awareness (Salvato et al., 2020; Suzuki et al., 2013; Tallon-Baudry et al., 2018). Visceral signals interact with the brain via multiple potential mechanisms (Azzalini et al., 2019; Craig, 2009; Tsakiris & Critchley, 2016). For example, the heart and stomach are intrinsic oscillators that generate their own constant electrical rhythm, sending continuous input of visceral information to the brain (Azzalini et al., 2019). These continuous visceral rhythms function in temporally compatible timescales with the brain, with the stomach oscillating at 0.05Hz and the cardiac cycle repeating every ~800ms (Rebollo et al., 2021). Thus, the constant temporally compatible input of internal electrical stimuli may constrain brain dynamics. Indeed, a widespread resting cortical network is coupled to the gastric rhythm, involving regions from multiple sensory modalities (Rebollo et al., 2018, 2021). Moreover, correlations of fluctuations in resting-state dynamics and heart rate variability have revealed a network coupled to the heart, including cingulate, insula, hippocampus, precuneus, and motor cortex (Rebollo et al., 2018; Thayer et al., 2012). Furthermore, respiration dynamics have been observed to entrain both local and global brain rhythms in rodents (Biskamp et al., 2017; Tort et al., 2018; Zhong et al., 2017) and humans (Heck et al., 2017; Herrero et al., 2017; Perl et al., 2019; Zelano et al., 2016). Therefore, visceral rhythms from multiple organs interact with brain dynamics, which would subsequently influence perceptual and cognitive processes.

The most extensively researched visceral component of cognition is brain-heart interactions. Thus, another interoceptive account of cognition focuses on cardiac activity, specifically, the firing of the baroreceptor in the aorta and carotid. The Baroreceptor Hypothesis states that during systole (i.e., cardiac contraction and ejection of blood), the baroreceptor is most active, which is thought to have an inhibitory effect on the central nervous system (Lacey, 1967; Rau et al., 1993). In contrast to during diastole (i.e., cardiac relaxation and filling of blood), when the baroreceptor is least active. This hypothesis originated from research demonstrating artificial baroreceptor activation induces sleep in cats, suggesting the baroreceptor dampens cortical processing during systole (Azzalini et al., 2019; Bonvallet et al., 1954). Indeed, pain perception and the startle reflex are reduced during systole (Schulz et al., 2009; Wilkinson et al., 2013). However, other cognitive processes such as somatosensory and visual detection show a facilitatory effect during systole (Edwards et al., 2009; Pramme et al., 2014, 2016), although there is conflicting evidence (Al et al., 2020; Park et al., 2014a; Salomon et al., 2016).

For more than a century, the body's physiological state has been described as a key component of emotional experience, such as in tradition James-Lange or Schachter and Singer appraisal theoretical accounts of emotion (Critchley & Garfinkel, 2017; Damasio et al., 1996; James, 1890, 1948; Schachter & Singer, 1962). Specifically, the cardiac cycle may facilitate the processing of threats and negative emotions (Garfinkel et al., 2014; Gray et al., 2012). For example, participants detected fearful faces at the threshold of conscious awareness more at systole and rated these as more intense than when presented at diastole (Garfinkel et al., 2014).

Furthermore, this corresponded to an increased amygdala activation to fearful faces during systole. Indeed, another study found participants rated facial expressions of disgust with higher intensity during systole in comparison to during diastole (Gray et al., 2012). Thus, the cardiac cycle may optimise the processing of threats by increasing heart rate and shortening diastole periods, potentially providing a short-term method of enhancing perception and cognition to threat (Azzalini et al., 2019; Critchley & Garfinkel, 2017). Overall, the cardiac cycle modulates various cognitive processes such as pain perception, sensory detection, and emotional processing, although more research is needed on the baroreceptors' inhibitory or facilitatory effects.

Another potential mechanism of viscera-brain interaction is via multisensory integration. In particular, embodied selfhood is thought to arise from the integration of somatosensory, proprioception, interoceptive and exteroceptive signals (Seth, 2013; Seth & Friston, 2016; Seth & Tsakiris, 2018). Indeed, research utilising body illusions has demonstrated the contribution of integrated cardiac signals with visual bodily-related stimuli for various self-cognitive phenomena. For example, pulsing a virtual limb or body in synchrony with the heartbeat enhances the sense of ownership and shifts the perceived location of self towards the simulated body/limb (Aspell et al., 2013; Heydrich et al., 2018; Suzuki et al., 2013). Furthermore, participants experience an increased sense of self-identification with another's face when synchronous cardiac stimulation is applied to a morphed self/others facial image (Sel et al., 2017). Importantly, individual ability to sense their heartbeat modulated self-cognitive experiences during these illusions. For example, during visual-tactile congruent stimulation with a rubber hand, the illusory sense of ownership negatively correlated with individual ability to sense their heartbeat (Tsakiris et al., 2011). However, during cardio-visual congruent stimulation, higher heartbeat perception was associated with an increased sense of ownership with a virtual hand (Suzuki et al., 2013). This may seem contradictory; however, lower heartbeat perception could increase focus to exteroceptive stimuli (visual-tactile) during the rubber hand illusion and subsequently increase susceptibility to an illusory sense of ownership. In contrast, the cardio-visual illusion may rely on an increased heartbeat perception to experience an interoceptive integrated body illusion. Furthermore, individual heartbeat perception increased linearly with a perceived similarity between a self and others facial image (Sel et al., 2017; Tajadura-Jiménez et al., 2012). Therefore, together, research utilising multisensory bodily illusions supports the role of integrated cardiac signals in self-cognitive mechanisms.

Finally, integrated interoceptive signals may contribute towards a unified first-person perspective by providing a subject-centred frame of reference of experience from the body (Park & Tallon-Baudry, 2014a; Tallon-Baudry et al., 2018). An embodied egocentric perspective is a core component of conscious experience, underlying pre-reflexive or minimal forms of selfhood such as the perceived sense of 'mineness' and unity of subjective experience (Gallagher, 2005; Limanowski & Blankenburg, 2013; Park & Tallon-Baudry, 2014). The continuous input of visceral signals to broad brain areas leads some to suggest that visceral input may act as an ideal binding agent for the formation of an integrated first-person viewpoint (Azzalini et al., 2019). Indeed, markers of cortical processing of the heartbeat (i.e., heart-evoked potential (HEP) amplitude) fluctuate with imagined perspective when comparing first-person imagination periods with third-person imagination (Babo-Rebelo et al., 2019). Furthermore, HEP amplitude co-varies with self-reported ratings of the first-person perspective nature of spontaneous thoughts, as well as the extent these thoughts were self-related (Babo-Rebelo et al., 2016). Thus, measuring neural processing of self-related visceral signals may provide a means of investigating self-related internal aspects of awareness, an under-researched but critical component of the DOC diagnostic criteria.

1.6 Measurement of Interoception

The most common method of studying individual perception of interoceptive stimuli is via heartbeat detection paradigms, including heartbeat tracking and heartbeat discrimination tasks. Tracking involves counting heartbeats for brief fixed time intervals without physically taking the pulse. The estimated number of heartbeats is compared with the actual frequency to calculate a cardiac perception score (McFarland, 1975; Schandry, 1981). Although tracking involves directly attending to heartbeat sensations, expectations of the general cardiac rhythm influence counting accuracy. In support, Ring and Brener (1996) observed heart rate prior beliefs were more predictive of heart rate during changes in posture and exercise than heartbeat counting task scores (Ring & Brener, 1996). In further support, Murphy et al (2018) found a relationship between heartbeat counting scores and intelligence and highlighted knowledge of the resting heart rate mediated this association. Moreover, individuals with a greater knowledge of their heart rate (i.e., athletes and medical professionals) demonstrated higher counting scores. Notably, their scores were significantly reduced when explicitly asked to include only felt heartbeats and not estimated heartbeats (Desmedt et al., 2018, 2020; Murphy et al., 2018). Furthermore, false heart rate feedback can change estimated heart rate beliefs without any actual heart rate changes (Ring et al., 2015). Thus, altogether, these studies support the influence of prior beliefs on heartbeat counting performance, and therefore, counting performance may not accurately reflect interoceptive ability and should be interpreted with caution. Zamariola et al (2018) investigated whether counting scores were unbiased by error types (i.e., under or overestimation) in a large sample (572) by correlating counting scores with the difference in actual and reported heartbeats. Heartbeat counting scores were primarily driven by underestimates of heart rate, with 95% reflecting underreports. In addition, the correlation of actual and reported heartbeats was very weak (r=.16) (Zamariola et al., 2018). Finally, for good heartbeat perceivers, it is impossible to distinguish between those who underreport least and those who overreport (i.e., 'hallucinate' heartbeats) (Corneille et al., 2020). Therefore, heartbeat counting scores are difficult to interpret, and alternative heartbeat detection tasks may be more appropriate (Corneille et al., 2020; Desmedt et al., 2020; Ring & Brener, 2018).

Discrimination tasks involve presenting a series of external stimuli (i.e., usually sounds) at a delay perceived as synchronous or asynchronous with the heartbeat. Participants who can accurately determine which stimuli are 'synchronous' with their heart are classified as good heartbeat perceivers (Brener et al., 1993a; Brener & Kluvitse, 1988a; Clemens, 1979; Whitehead et al., 1977; Yates et al., 1985). However, the experimenter assumes the timing of the perceived synchronous and perceived asynchronous delays. Generally, heartbeat sensations are considered to be perceived at a short delay from the heartbeat (i.e., during ventricular contraction/systole). Thus, a short cardio-audio delay is employed for the perceived synchronous condition (i.e., signal plus), whereas a longer delay from the heartbeat (i.e., during cardiac relaxation/diastole) is considered a period of absent heartbeat sensations and thus, defines the perceived asynchronous condition (i.e., signal minus). The Method of Constant Stimuli (MCS) expands from traditional two-interval discrimination tasks to encompass six intervals from the heartbeat (Brener et al., 1993a; Brener & Ring, 2016). Although this multi-interval task demonstrated a mode preferred interval of ~200-250ms post-R-peak (as used in recent two-interval heartbeat discrimination tasks (Garfinkel et al., 2015; Hart et al., 2013; Palser et al., 2018)), good heartbeat perceivers showed considerable individual differences in their median preferred interval of heartbeat perception (i.e., 131-373ms) (Brener et al., 1993a; Brener & Ring, 2016; Ring & Brener, 1992). Thus, two-interval tasks may not accurately determine interoceptive performance if the 'perceived synchronous' delay does not correspond to the timing of each individual's heartbeat sensations. A multi-interval discrimination task can be initially employed to determine the time of individual heartbeat perception. Subsequently, individual differences in the median preferred interval (i.e., perceived synchronous delay - calculated from the distribution of interval choices) can be inputted into a subsequent two-interval task. In two previous studies, interoceptive performance in a two-interval task was significantly improved when the delays were individually adjusted (Brener & Kluvitse, 1988b; Mesas & Chica, 2003). Thus, two-interval discrimination tasks may more accurately determine interoceptive performance if individually adjusted using an initial multi-interval task.

Performance on these tasks involves distinct mechanisms with tracking encompassing internal monitoring and discrimination entailing interoceptive-exteroceptive multisensory integration; therefore, tracking and discrimination performance is not always correlated, with a meta-analysis revealing a shared variance of only 4.4% between tasks (Garfinkel et al., 2015; Hickman et al., 2020; Kleckner & Quigley, 2015; Ring & Brener, 2018). Although discrimination tasks measure interoception indirectly via multisensory integration, measuring interoceptive-exteroceptive integrative ability is advantageous as it underlies crucial aspects of conscious experience such as the generation of a first-person perspective and embodied selfhood (Azzalini et al., 2019; Gallagher & Zahavi, 2012; Tallon-Baudry et al., 2018). Thus, the multisensory heartbeat discrimination task is ideal for measuring interoception associated with internal aspects of awareness. In addition to interoceptive accuracy, Garfinkel et al (2015) proposed two additional distinct and dissociable elements of interoception: interoceptive sensibility and interoceptive awareness. Interoceptive sensibility describes the subjective self-evaluated perception of internal sensations and the ability to detect those sensations. Traditionally, experimenters assess sensibility via self-report body perception questionnaires or heartbeat detection confidence ratings. Interoceptive awareness examines the compatibility of objective interoceptive accuracy scores with subjective interoceptive sensibility measures. If interoceptive accuracy and sensibility are highly correlated (they're a good heartbeat perceiver and aware of it), they will have high metacognitive interoceptive awareness (Garfinkel et al., 2015). These objective, subjective and metacognitive facets of interoception influence cognitive processes differently, and thus, measuring separate interoceptive indices ensures all dimensions of interoception are characterised (Forkmann et al., 2016; Garfinkel et al., 2015; Nusser et al., 2020; Slotta et al., 2021).

Critchley et al (2004) used fMRI during a heartbeat discrimination task to assess the neural correlates of interoception. The experiment involved presenting tones immediately after the participant's pulse detected at the fingertip (perceived synchronous), or with a 500ms delay (perceived asynchronous), with deviant tones of different pitch interspersed. Note, there is a delay from the ECG R-peak (i.e., heartbeat) detected at the chest and the pulse detected at the fingertip. Therefore, there was a short delay from the heartbeat in the 'immediate' condition (as in heartbeat discrimination tasks). They manipulated participant's attention to focus on the internal (heart-related) or external (pitch-related) quality of the tones (Critchley et al., 2004). Directing attention internally resulted in enhanced activity in the insula, somatomotor region, and cingulate cortices. Grey matter volume and activity in the right anterior insular cortex predicted interoceptive accuracy on the heartbeat detection task and correlated with subjective ratings of visceral awareness and emotional experience. Indeed, the insula is often depicted as the primary interoceptive cortex, as it receives viscerosensory input from several internal organs (Stephani et al., 2011; Uddin et al., 2017; Wilson-Mendenhall et al., 2019). Craig (2009) collated research demonstrating the involvement of the insula in various conscious processes such as self-recognition, emotional awareness, momentary visual and auditory awareness, error awareness, temperature perception, and time perception. Subsequently, Craig suggested that the insula and its bilateral frontal connections underlies reflective self-awareness and subjective feeling states via interoception. Specifically, Craig proposes that bodily state representations are sent to the posterior insular cortex via the laminar I primary thalamocortical pathway, while the connecting anterior insular cortex encompasses re-representations of these bodily states. These insula re-representations provide the foundation for subjective feeling states and a first-personal perspective, explaining its broad activation in numerous conscious cognitive processes (Craig, 2009). Finally, the insula is incorporated into an extensive interoceptive network, comprised of viscerosensory neural afferents, arriving at the brainstem and thalamus via the dorsal root ganglion and vagus nerve, outputting to the hypothalamus, amygdala, anterior cingulate cortex, and insula. The highest interoceptive regions include the posterior ventral medial prefrontal cortex and the orbitofrontal cortex (see Figure 2) (Craig, 2009; Critchley & Harrison, 2013; Damasio & Carvalho, 2013).

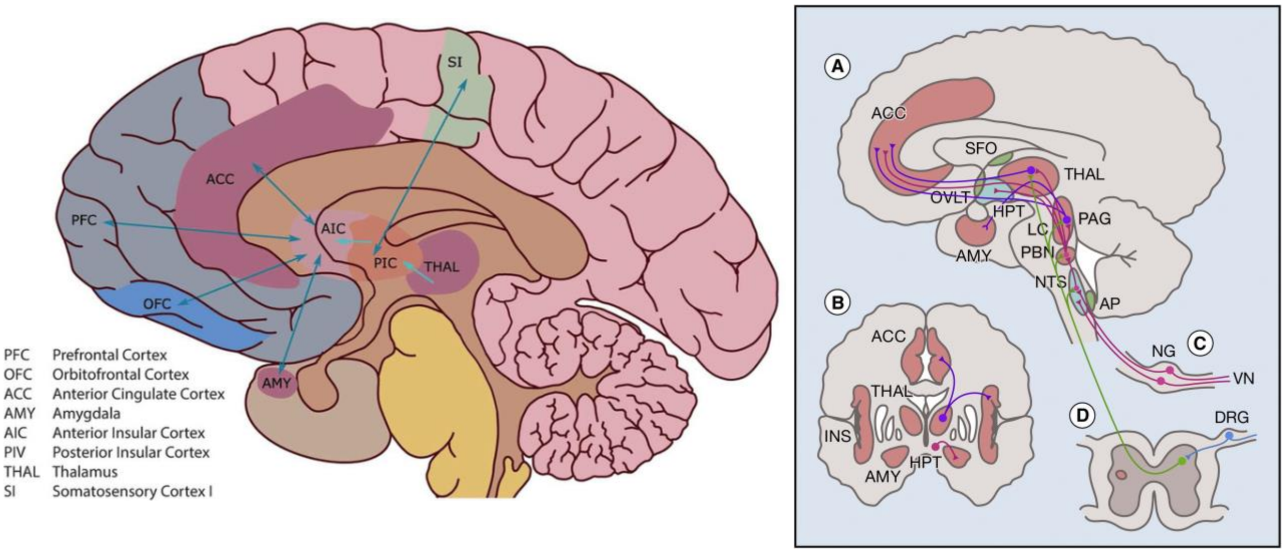

Figure 2. Diagrams of the interoceptive network. [Left] Connectivity of the anterior and posterior insular cortex (AIC and PIC), extracted from Quadt et al., 2018. [Right] Pathways of the interoceptive network, extracted from Critchley & Harrison., 2013. (A) parasagittal cortical slice, (B) coronal cortical slice, (C) vagus nerve nodose ganglion, (D) spinal cord. DRG=dorsal root ganglion, THAL=thalamus, NTS=nucleus of the solitary tract, PB=parabrachial nucleus, PAG=periaqueductal gray matter, VN=vagus nerve, NG= nodose ganglion, HPT=hypothalamus, AMY=amygdala, ACC=anterior cingulate cortex, INS=insula, LC=locus coeruleus, AP=area postrema, OVLT=organum vasculosum of lamina terminalae (OVLT) and SFO=subfornical organ.

1.7 Interoceptive Predictive Coding

Seth et al (2012) proposed an interoceptive predictive coding model of conscious presence, a core aspect of self-consciousness (Metzinger, 2003; Seth et al., 2012). This model incorporates interoception into the framework of predictive coding to explain subjective feeling states such as emotion and presence (Seth, 2013). The predictive coding framework is a unifying theory of cognition, depicting the brain as a probabilistic machine with generative models that infer the cause of sensory inputs. These probabilistic models function hierarchically, with top-down predictions from higher-level brain regions (i.e., priors) constantly compared with incoming lower-level sensory representations. Any differences between the two signals are propagated up the hierarchy as prediction error, iteratively updating the higher-level model representations (Rao & Ballard, 1999). This framework proposes the core function of the brain is to minimise prediction error via the interaction of adjacent prediction and sensory input signals at each hierarchical level. Perception is formed from the global resolution of prediction error across the brain, reflecting a deep encoded multi-layered explanation of the cause of sensory inputs. The brain operates two major mechanisms of minimising prediction error: either models are updated to accommodate unexpected signals (i.e., perceptual inference, reflecting learning over time) or actions are performed to better match predictions (i.e., active inference, potentially accounting for adaptive behaviour and control) (Adams et al., 2013; Friston, 2010; Millidge et al., 2021).

Furthermore, precision modulates predictive mechanisms by weighting prediction error signals. Precision formally represents the inverse of the variance of the probability distributions, and therefore uncertainty of the signal. Attention optimises the precision-weighting of sensory signals by defining their relative precision weight both within and between modalities via synaptic gain control mechanisms (Friston, 2009). For example, attending to a specific sensory modality will enhance the precision of associated predictive signals, than other modalities (Hohwy, 2012). Within modalities, the relative precision of prediction and prediction error signals at each level determines the method of prediction error minimisation. For example, if prediction errors are weighted with higher precision than the priors, it suggests prediction errors are more informative, and thus prediction errors will update models. In contrast, decreased precision of prediction errors in comparison to the priors (i.e., suggests prediction errors reflect noise) will result in predictions dominating, and thus predictions will be facilitated via action or perception (Ainley et al., 2016; Seth & Tsakiris, 2018).

There is a vast amount of evidence for predictive coding, including studies investigating ERP responses to unexpected stimuli. For example, the MMN responses (i.e., difference wave of *deviant* minus *standard* auditory responses) emphasises a characteristically larger response to unexpected stimuli than expected stimuli (Heilbron & Chait, 2018; Näätänen, 2003). Similarly, the N400 response reflects a larger ERP to semantically unexpected words than expected words (i.e., he spread the warm bread with *socks* compared to *butter* – difference wave of ERP in response to *socks* than *butter*). The interpretation of MMN and N400 responses are consistent with a larger prediction error signal to unexpected stimuli (i.e., predictions are not matched to incoming sensory input), supporting predictive coding frameworks (Heilbron & Chait, 2018; Mantegna et al., 2019). Furthermore, omission responses (i.e., during periods of silence when a sound was expected) provide direct evidence of top-down predictions, as the brain exhibits predictive responses in the absence of bottom-up sensory input (Heilbron & Chait, 2018). In support, dynamic causal modelling (DCM) provides evidence of unexpected auditory omission responses, revealing top-down driving inputs from bilateral inferior frontal gyrus (Chennu et al., 2016). Moreover, in support of attention as a mechanism of precision-weighting, attention enhanced the amplitude of omission responses, and DCM demonstrated this operated via strengthened downward connections (Chennu et al., 2016). However, contrary to predictive coding frameworks, not all responses are modulated by precision, such as the pre-attentive MMN response (Garrido et al., 2009).

Equally, not all ERP responses are compatible with predictive coding accounts, such as when large ERPs are elicited from expected stimuli. For example, in a rapid serial visual presentation (RSVP) task, participants are asked to identify a target in a stream of fast presented stimuli (i.e., 10 stimuli per second) (Bowman et al., 2015; Bowman, Filetti, Janssen, et al., 2013). The salient target stimuli elicit a large P3 response in comparison to non-salient distractors. This is inconsistent with predictive coding as target predictions are matched with the sensory input, thus, prediction error should be zero (or very small if arguing there is always some prediction error). Conversely, some argue attention towards the expected target enhances precision which results in a large ERP. Although this is possible, the over-reliance on precision for describing antipredictive effects presents the concern that predictive coding may be unfalsifiable. Furthermore, precision is thought to mechanise by multiplicity. Therefore, precision multiplied by zero prediction error would have no effect, or if arguing a very small prediction error, this would need to be multiplied significantly (i.e., by very high precision) to be noticeable. Finally, a stimulus weighted with high precision proposedly determines model updating. However, correctly predicted stimuli shouldn't update accurate models as this would be an inefficient neural process (Bowman et al., 2015; Bowman, Filetti, Wyble, et al., 2013). Thus, the brain might be better described as functioning with predictive and antipredictive (i.e., salience) mechanisms rather than a unifying predictive theory.

Initially, predictive coding was applied solely to exteroceptive perception such as vision or audition. Interoceptive predictive models emerged, which followed the same principles as traditional exteroceptive models. For example, at low levels of the predictive hierarchy, models depict interoceptive sensory experience arising from inferences regarding the cause of viscerosensory inputs. At higher levels of the hierarchy, interoceptive predictive mechanisms represent complex emotional experiences and the sense of conscious presence. For example, Seth et al (2012; 2013) proposed an interoceptive predictive coding model of conscious presence and emotional experience (see Figure 3). Conscious presence is the subjective sense of reality and the sense of existing as a self within that reality, essentially, the sense of being present *now* in reality as a self. Seth's model includes two primary components which contribute towards conscious presence: a presence and agency component, each including a state (i.e., generation of predictive and control signals) and an error (computation of prediction error signals) module. The presence component interacts primarily with the interoceptive autonomic systems, and the agency component interacts with the sensorimotor system (Marshall et al., 2018; Seth et al., 2012). The sense of presence and agency is proposed to be achieved by successfully suppressing interoceptive or sensorimotor prediction errors. Specifically, error minimisation is accomplished by successfully predicting interoceptive inputs or performing visceral responses that match interoceptive predictions (i.e., via interoceptive predictions setting autonomic reference points for homeostatic responses) (Adams et al., 2013; Seth, 2013). Seth's interoceptive predictive model emphasises the interaction of interoceptive predictive mechanisms with sensorimotor systems, which govern the sense of agency for conscious presence. Specifically, interoceptive predictions are influenced by the state of both sensorimotor and autonomic components, and interoceptive prediction error is sent to both state modules (Seth et al., 2012). This is supported by research that shows that dysfunctions in agency (i.e., schizophrenic delusions of control) and presence (i.e., depersonalisation) often co-occur (Ruhrmann et al., 2010). Furthermore, employing an interactive virtual environment (i.e., increased agency) enhances the sense of presence in virtual reality, than passively observing (Gutiérrez-Martínez et al., 2011). Thus, an integrated model of interoceptive (i.e., underlying presence) and exteroceptive (i.e., underlying agency) signals may be a key component of selfhood.

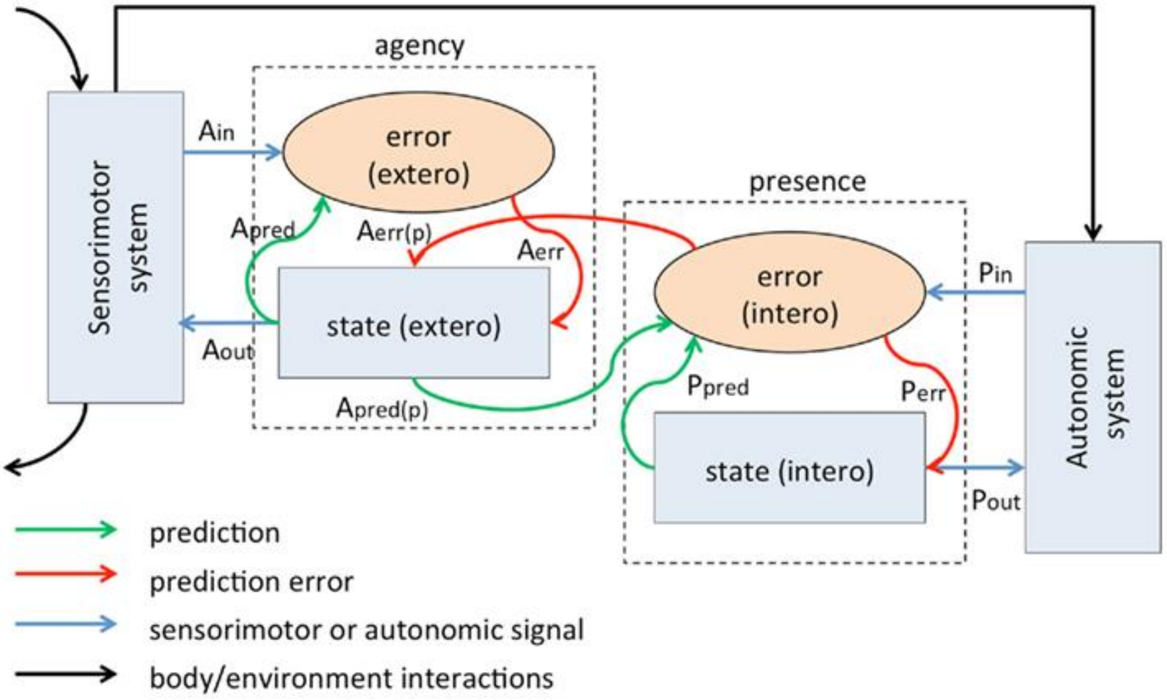

Figure 3. *Interoceptive predictive coding model of conscious presence, extracted from Seth et al., 2012.*

Seth et al (2012) emphasises the anterior insula cortex (AIC) and anterior cingulate cortex (ACC) as key cortical regions for interoceptive predictive coding. Specifically, the AIC is proposed to be a comparator region for interoceptive predictions and error signals (Bossaerts, 2010; Preuschoff et al., 2008; Seth, 2013; Seth et al., 2012). The embodied predictive interoceptive coding (EPIC) model expands this viewpoint to encompass multiple pathways in a predictive interoceptive cortical network (Barrett & Simmons, 2015). Specifically, the EPIC model describes interoceptive predictions arising from neurons in deep agranular visceromotor cortices with less laminar differentiation (i.e., the medial cerebral wall encompassing mid-to-anterior cingulate cortex, posterior ventromedial prefrontal cortex, orbitofrontal cortex, and anterior insular cortex). Interoceptive predictions are sent to granular sensory cortices of the mid-to-posterior insula. While prediction error neurons in the granular (i.e., greater laminar differentiation) mid-to-posterior insula compute the difference between predicted & received sensory input. Precision cells reside in multiple layers of granular and agranular cortices to adjust the gain of prediction and prediction error signals dynamically (Barrett & Simmons, 2015). Barrett & Simmons (2015) highlight rich connections in the AIC and ACC (i.e., 'rich club' hubs) with other highly connected networks such as the intrinsic control and attention networks (van den Heuvel & Sporns, 2011). Thus, the AIC and ACC may send interoceptive information to other networks to modify cognitive and behavioural responses for homeostasis and allostasis. Furthermore, the AIC is a core region for interoceptive and exteroceptive integration (Sepulcre et al., 2012; Simmons et al., 2013). The multisensory and richly connected AIC makes an ideal hub for generating a subjective multisensory representation of the body within the world (i.e., embodied selfhood) (Barrett & Simmons, 2015). In support, patients with a dysfunctional sense of presence and self-processing (i.e., depersonalisation disorder) have abnormal insula functioning (Phillips et al., 2001; Sierra & David, 2011).

More recent interoceptive predictive coding models describe the role of interoceptive mechanisms in other facets of selfhood such as self-recognition, body-ownership, minimal self-awareness, and a metacognitive global sense of self (Allen & Friston, 2018; Allen & Tsakiri, 2019; Apps & Tsakiris, 2014; Limanowski & Blankenburg, 2013). Apps and Tsakiris (2014) describe self-recognition (i.e., recognising one's voice or facial features as ourselves) as arising from minimising free energy or error in several sensory systems. Over time, auditory and visual predictions become congruent with bodily predictions, creating a multimodal self-representation. This self-recognition model further emphasises the importance of interoceptive-exteroceptive integration for self-cognition. Interestingly, primary visceral cortices of the insula and cingulate areas are highly multisensory compared to other primary sensory regions, which are much more unimodal (i.e., vision/audition) (Sepulcre et al., 2012; Simmons et al., 2013). Allen's and Tsakiris's (2019) interoceptive self-modal also accentuate the importance of interoceptive-exteroceptive integration for the identification of sensations as originating from 'me'. In particular, they describe exteroception as contributing towards the malleability of body representation and interoception for the stability of body awareness. Interoception is thought to be particularly important for self-stability because it underpins autonomic reflexes, which regulate homeostasis and allostasis (Kleckner et al., 2017). Importantly, homeostatic and allostatic regulation involves maintaining healthy levels of life-sustaining physiological variables, which ensures a stable and predictable visceral environment (Seth & Tsakiris, 2018). Thus, the low variability (i.e., high precision) of internal states preserves self-identity as visceral signals provide a continuous and precise estimate of the state of the body (Allen & Tsakiri, 2019; Seth & Tsakiris, 2018). In other words, the body provides a continuous and predictable input to the brain and, thus, is an ideal constant vehicle for subjective self-experience (Limanowski & Blankenburg, 2013).

1.8 Neural Marker of Interoceptive Processing: Heart Evoked Potentials

Neuronal processing of cardiac interoceptive predictive mechanisms can be measured by averaging electrophysiological signals time-locked to heartbeats (i.e., typically the ECG R-peak), producing heart-evoked potentials (HEPs) (Pollatos & Schandry, 2004; Schandry et al., 1986). HEPs are thought to represent cortical processing of cardiac activity and are primarily observed over frontocentral channels (Babo-Rebelo et al., 2016; Canales-Johnson et al., 2015; Montoya et al., 1993; Petzschner et al., 2019), although parietal HEP effects have also been observed (Babo-Rebelo et al., 2016; Sel et al., 2017). Likewise, the HEP has been detected over broad temporal scales (i.e., 150 to 600ms post-R-peak) (Babo-Rebelo et al., 2016; Petzschner et al., 2019; Pfeiffer & De Lucia, 2017). The HEPs wide-ranging spatial and temporal observation may partially result from an extensive contributing interoceptive network, which is recruited differently depending on the task/cognitive process/clinical condition investigated. Moreover, the HEP has vast potential contributing sources, including baroreceptor firing in arteries, cardiac afferent neurons, somatosensory mapping through the skin, and neurovascular coupling (Park & Blanke, 2019). Furthermore, there is a lack of standardised preprocessing and analysis HEP procedures, including reference location, baseline correction, and method of CFA correction, all influencing the spatial and temporal extent of HEP effects (Coll et al., 2021a). The lack of standardised procedures and HEP variability has led to some question whether the HEP reflects cortical interoceptive processing or is a result of confounds. However, intracranial research revealed HEP activity without CFA contamination, providing concrete evidence of the existence of HEPs (Park & Blanke, 2019). Moreover, the high spatial resolution of intracranial electrodes enabled the identification of HEP sources. Specifically, surface intracranial grid electrodes reveal HEPs in the somatosensory cortex (Kern et al., 2013). Intracranial depth electrodes revealed the insula, opercular region, inferior frontal gyrus, and amygdala (Park et al., 2018).

CFA correction is essential to ensure HEPs reflect cortical activity rather than electrical influences from the heart itself. CFA correction is particularly important if cardiac differences between conditions/groups exist, inserting artefactual HEP differences. Thus, in addition to CFA correction, control analyses with ECG, heart rate, and heart rate variability are often completed in parallel to remove the possibility of cardiac activity confounds. CFA correction methods include ICA, rest/nose template subtraction, Hjorth source derivation, current source density transformation, or the time window is restricted to a period of minimal CFA-influences (typically R-peak+455-595ms – during cardiac relaxation/diastole) (Coll et al., 2021a). However, CFA correction is challenging, as it is difficult to determine if the CFA has been eradicated or even if the HEP cortical effect of interest has been removed as a consequence. For example, subtracting a rest template of HEP activity may not completely remove the CFA due to inter-trial variability in latency. Furthermore, control analyses without CFA correction are necessary to ensure the correction method did not insert artificial effects by removing CFA influences more in one condition/group than another. Therefore, analysing neural responses locked to cardiac activity is a challenge, but valuable conclusions can be drawn if thorough control analyses and correction methods are completed.

Pfeiffer and De Lucia (2017) investigated differences in HEP responses during omission periods (i.e., missing stimuli) presented within cardiac synchronous or asynchronous auditory tone sequences (Pfeiffer & De Lucia, 2017). Omission responses are an elegant method of measuring pure top-down predictive signals without contaminating bottom-up auditory input (Chennu et al., 2016; Wacongne et al., 2011). This is because prediction error is thought to be computed by subtracting sensory input from prediction signals. While omission responses are defined as periods of no bottom-up sensory input (i.e., a period of silence). Thus, there is no bottom-up sensory input to subtract, leaving pure top-down prediction signals (Heilbron & Chait, 2018). Pfeiffer and De Lucia (2017) found an increased HEP amplitude during omission periods presented in cardiac synchronous sound sequences than during omissions within cardiac asynchronous sequences. This suggests the brain integrated the cardiac and auditory information to predict upcoming sounds synchronous with the heartbeat. The authors interpret this effect as a ‘surprise response’ reflecting increased prediction error from expecting a sound during synchronous stimulation. However, it is difficult to explain how neurons may compute prediction errors in the absence of bottom-up input. Thus, instead, the effect may represent a larger cardio-audio integrated expectation during synchronous sound sequences. It is possible omission responses could reflect prediction error if a memory template is subtracted from prediction signals. However, Bendixen et al (2009) showed that omission responses were only observed when a second tone was occasionally omitted, not the first of a series of sounds, suggesting omission responses are not a result of comparisons with a memory template. However, this study only looked at responses with short latencies of <50ms. Thus, later omission effects may have evidenced a memory template mechanism.

van Elk et al (2014) similarly investigated cardiac-auditory predictions by presenting sounds at various intervals locked to the heartbeat (Rpeak+0ms, +100ms, +200ms, +300ms, +400ms, +500ms) and compared auditory N1 responses across the delay conditions. With CFA correction, there were no significant N1 differences across cardio-audio delay conditions. However, to increase power, they collapsed all cardio-audio delay conditions into a single heartbeat-related sounds condition. Heart-related sounds produced a reduced N1 component than externally generated sounds, suggesting cardiac-related predictions reduced the prediction error in the auditory responses. However, this was only marginally significant with CFA correction ($p = .07$). Thus, this study further supports the existence of integrated cardiac-auditory predictive mechanisms but highlights the importance of CFA correction to control for artefactual cardiac influences.

If integrated cardiac-auditory predictive mechanisms operate under a predictive coding framework, interoceptive responses should be modulated by precision-weighting. Attention is one mechanism proposed to function via precision optimisation (Hohwy, 2012). In support, multiple studies have highlighted attentional modulation of HEP amplitude (García-Cordero et al., 2017; Judah et al., 2018; Mai et al., 2018; Montoya et al., 1993; Petzschner et al., 2019; Salamone et al., 2018; S. M. Schulz, 2016; Villena-González et al., 2017; Yuan et al., 2007). The majority of these studies compared HEPs during the heartbeat counting task (i.e., internal/heartbeat attention) with HEPs during an external control condition or rest. A meta-analysis of 11 attention-HEP studies revealed a strong significant effect of attention on HEP amplitude, with the strongest effect 350-400ms at frontocentral electrodes (Coll et al., 2021a). These studies identify a larger HEP amplitude when attending to internal cardiac sensations than external stimuli or rest. This supports the precision-weighting properties of prediction coding frameworks. Specifically, predictive coding suggests attending internally weights interoceptive signals with higher precision than other modalities, resulting in larger HEP responses than when attending externally. These studies revealed the influence of attentional-precision on direct interoceptive attention in isolation (i.e., during heartbeat counting tasks). The effect of precision on interoceptive-exteroceptive integration is unknown (i.e., during cardiac-auditory heartbeat discrimination tasks). Understanding the mechanistic account of interoceptive-exteroceptive integration is crucial as it underlies the generation of a first-person perspective and embodied selfhood (Heydrich et al., 2018; Sel et al., 2017; Suzuki et al., 2013; Tallon-Baudry et al., 2018). Thus, identifying attentionally-modulated interoceptive-exteroceptive responses may provide evidence of top-down internal self-related aspects of awareness, a much-needed signature for DOC patients.

Individual differences in interoceptive ability can similarly be viewed as variations in precision. Indeed, numerous studies reveal the influence of interoceptive accuracy via heartbeat counting tasks on HEP responses (Canales-Johnson et al., 2015; Mai et al., 2018; Montoya et al., 1993; Pollatos & Schandry, 2004; Schandry & Weitkunat, 1990). A meta-analysis identified a moderate influence of interoceptive counting performance on HEP amplitude, with the strongest effect 250ms in central and frontocentral channels (Coll et al., 2021a). Similarly, HEP amplitudes were larger for those with high interoceptive counting ability than those with low counting performance, which can be interpreted as levels of trait precision. However, less research has been conducted on the influence of interoceptive-exteroceptive integrated heartbeat discrimination performance. This is particularly important as heartbeat counting tasks are subject to multiple confounds, such as prior knowledge of the heart rate and time estimation ability (Corneille et al., 2020; Desmedt et al., 2020; Murphy et al., 2018; Ring & Brener, 1996, 2018; Zamariola et al., 2018). Thus, previous research on heartbeat counting performance may not accurately determine the influence of interoceptive ability on HEP responses. Furthermore, research is needed on the impact of all dimensions of interoceptive performance on HEPs to ensure subjective, objective, and metacognitive aspects are characterised.

HEPs are ideal for clinical prognostic use because they can be observed at the bedside non-invasively using EEG. Indeed, HEPs have been associated with numerous conscious and self-processing aspects of cognition, providing potential as a marker of internal self-related aspects of awareness. For example, HEPs predict the conscious perceptual detection of somatosensory and visual stimuli (Al et al., 2020; Park et al., 2014). Moreover, HEPs fluctuate with ratings of the self-relatedness and first-person content of spontaneous thoughts (Babo-Rebelo et al., 2016). Additionally, HEPs co-vary when comparing periods of imagining oneself from a first-person perspective with the imagination of a familiar other from a third-person perspective (Babo-Rebelo et al., 2019). Finally, HEPs correlate with an illusory sense of body ownership with a virtual body during a full-body illusion (Park et al., 2016, 2018). Therefore, HEPs may provide an ideal signature of self-awareness for prognosis in DOC patients. In support, recent evidence has demonstrated the diagnostic utility of HEPs (Candia-Rivera et al., 2021; Raimondo et al., 2017). For example, Raimondo et al (2017) highlighted two HEP component differences between MCS and VS/UWS patients; an early (i.e., 144-340ms) CFA-like difference component, followed by a central positivity HEP difference (i.e., 340-540ms). However, this study did not apply CFA correction; thus, differences may reflect cardiac activity influences rather than high-level neural differences. Using a machine learning approach, Candia-Rivera et al (2021) compared CFA-corrected HEP responses across VS/UWS and MCS consciousness diagnoses. HEP amplitude and variance differentiated VS/UWS and MCS diagnoses with high accuracy (accuracy 87%, sensitivity 96%; specificity 50%) (Candia-Rivera et al., 2021). Despite diagnostic evidence of HEPs in chronic disorders of consciousness, no research has been conducted on the prognostic value of HEPs in acute unresponsive patients. This is important as prognostic research has implications for critical care decisions such as rehabilitation and life-support decisions. Indeed, previous research demonstrated that early detection of consciousness predicts functional recovery at one year (Claassen et al., 2019). This could be because there is a critical window of opportunity where interventions are most effective (Kitzinger & Kitzinger, 2013). Thus, the early detection of HEPs in acute patients may predict the recovery of internal self-related aspects of awareness.

1.9 Thesis Outline

Overall, a wealth of research indicates the involvement of interoceptive-exteroceptive integration in subjective emotional and self-cognitive experiences, including forming a unified first-person perspective. Furthermore, cortical processing of the heartbeat (i.e., HEPs) fluctuates with numerous conscious self-related aspects of awareness, including differentiating between consciousness state diagnoses. Thus, my thesis investigates interoceptive-exteroceptive integrative mechanisms reflected in HEPs to provide a signature that underlies internal self-related aspects of awareness, a critically under-researched component of the consciousness diagnostic criteria. First, I characterise mechanisms of interoceptive-exteroceptive integration reflected in HEPs during an integrated heartbeat detection and omission detection task. Specifically, I determine if these cross-modal integrated mechanisms operate under a predictive coding account. Thus, I assess the contribution of precision (state precision via attention and trait precision via interoceptive ability) to integrated predictive mechanisms. Second, I ensure our heartbeat detection task accounts for individual temporal differences in heartbeat perception to determine the influence of trait precision on cross-modal predictive mechanisms more accurately. Finally, I apply neural signatures of interoceptive processing – HEPs - for prognosis from acute unresponsive states, potentially by investigating preserved internal self-awareness mechanisms. Finally, my thesis concludes with a general discussion of experimental findings.

My thesis has three important hypotheses:

1. Interoceptive (cardiac) signals will drive expectations of exteroceptive (auditory) stimuli. Thus, we predict mechanisms of interoceptive-exteroceptive integration operate predictively.
2. Integrated cardio-audio predictive mechanisms will be modulated by state (i.e., attention) and trait (i.e., interoceptive ability) measures of precision.
3. Resting HEPs and cardiac measures will provide prognostic promise of predicting recovery from acute unresponsive states, potentially via demonstrating intact self-cognitive mechanisms.

CHAPTER 2: SIGNATURES OF INTEROCEPTIVE-EXTEROCEPTIVE INTEGRATION[1]

2.1 Abstract

Several theories propose that emotions and self-awareness arise from the integration of internal and external signals and their respective precision-weighted expectations. Supporting these mechanisms, research indicates that the brain uses temporal cues from cardiac signals to predict auditory stimuli, and that these predictions and their prediction errors can be observed in the scalp heartbeat-evoked potential (HEP). We investigated the effect of precision modulations on these cross-modal predictive mechanisms, via attention and interoceptive ability. We presented auditory sequences at short (perceived synchronous) or long (perceived asynchronous) cardio-audio delays, with half of the trials including an omission. Participants attended to the cardio-audio synchronicity of the tones (internal attention) or the auditory stimuli alone (external attention). Comparing HEPs during omissions allowed for the observation of pure predictive signals, without contaminating auditory input. We observed an early effect of cardio-audio delay, reflecting a difference in heartbeat-driven expectations. We also observed a larger positivity to omissions of sounds perceived as synchronous than to omissions of sounds perceived as asynchronous when attending internally only, consistent with the role of attentional precision for enhancing predictions. These results provide support for attentionally-modulated cross-modal predictive coding, and suggest a potential tool for investigating its role in emotion and self-awareness.

Keywords:

Attention, expectation, interoception, predictive coding, precision.

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[1] As published in:
Banellis, L., & Cruse, D. (2020). Skipping a beat: heartbeat-evoked potentials reflect predictions during interoceptive-exteroceptive integration. *Cerebral Cortex Communications*, *1*(1), tgaa060. https://doi.org/10.1093/texcom/tgaa060 (Includes slight differences due to PhD corrections).

2.2 Introduction

The Bayesian brain hypothesis states that the brain is a probabilistic machine, with hierarchical neuronal representations underlying cognition, perception, and behaviour (Friston, 2009). The predictive coding framework posits that, in the comparison between top-down predictions from high-level brain regions and incoming low-level sensory input, any difference between the two signals is propagated up the hierarchy as a prediction error, thus allowing for iterative updating of the higher-level representations (Rao & Ballard, 1999). Successful matching of predictions with incoming stimuli, and thus successful minimisation of prediction error, results in 'correct' perception, cognition, and action (Friston, 2010). Minimisation of prediction error is accomplished either by updating predictive models to accommodate unexpected signals (i.e. perceptual inference) or by performing actions (such as motor or autonomic responses) to better match predictions (i.e. active inference) (Adams et al., 2013; Friston, 2010) consistent with an embodied view of cognition (Allen & Friston, 2018).

As with perception of external stimuli (exteroception), perception of internal stimuli (interoception) is also considered to be supported by hierarchical prediction error minimisation mechanisms (Barrett & Simmons, 2015; Seth, 2013; Seth et al., 2012). Broadly, interoception is the perception of visceral bodily sensations such as heartbeat contractions, the expansion of lungs, or feelings of the body's internal state such as hunger or nausea (Cameron, 2001; Sherrington, 1952). The Embodied Predictive Interoceptive Coding (EPIC) model describes an interoceptive cortical network comprising of viscerosensory neural afferents which arrive at the brainstem and thalamus via the dorsal root ganglion and vagus nerve, outputting to the hypothalamus, amygdala, anterior cingulate cortex and the insula, with its highest regions residing in the posterior ventral medial prefrontal cortex (vmPFC) and the orbitofrontal cortex (Barrett & Simmons, 2015; Critchley & Garfinkel, 2018; Critchley & Harrison, 2013; A. Damasio & Carvalho, 2013; Quadt et al., 2018). This network is thought to be involved in numerous high level cognitive processes such as emotional processing, bodily self-consciousness, visual awareness, self-recognition, attention and time perception (Azzalini et al., 2019; Craig, 2009; Critchley & Harrison, 2013; Quadt et al., 2018; Tsakiris & Critchley, 2016). Indeed, as part of a prediction error minimisation framework, Seth et al (2012; 2013) have proposed that embodied selfhood and emotional experience are the outcome of successful suppression of interoceptive prediction errors through active inference (Seth & Friston, 2016). Additionally, dysfunctional interoceptive predictive mechanisms have been proposed to account for a variety of psychological disorders such as anxiety, depression, autism, dissociative disorders, and psychotic illnesses (Haker et al., 2016; Quattrocki & Friston, 2014; Seth et al., 2012; Seth & Friston, 2016), thus increasing scientific interest in characterising these mechanisms.

One potential method of investigating the neural basis of interoceptive predictive mechanisms is by analysing heart-evoked potentials (HEPs) (Pollatos & Schandry, 2004; Schandry et al., 1986). HEPs are averaged electrophysiological signals time-locked to heartbeats and are thought to reflect neuronal processing of cardiac afferents. The HEP can be interpreted to reflect sensory cardiac processing or associated cognitive processes such as emotion and selfhood (Park & Blanke., 2019). Under a predictive coding framework, the HEP can be interpreted to encompass interoceptive prediction error of each individual heartbeat (Ainley et al., 2016; Petzschner et al., 2019). In a recent study on interoceptive predictions, Pfeiffer & De Lucia (2017) presented healthy participants with a sequence of tones that were either synchronous or asynchronous with their own heartbeat (Pfeiffer & De Lucia, 2017). Crucially, the occasional tone was unexpectedly omitted from these sequences. Evoked responses to expected sounds that did not happen – i.e. omission responses – are an elegant way of observing pure prediction signals without the contamination of auditory potentials (Chennu et al., 2016; Wacongne et al., 2011). Consequently, Pfeiffer & De Lucia (2017) reported a larger HEP during omission periods in cardiac synchrony, relative to cardiac asynchrony, consistent with a predictive account in which the brain uses the interoceptive (cardiac) signals to predict upcoming exteroceptive signals (sounds).

Predictions and their errors are also influenced by their precision – formally, the inverse of the variance, or the uncertainty in the signal. Within the prediction error minimisation framework, attention is described as a means to optimise the relative precision weight of predictions and prediction error signals, via synaptic gain control (Friston, 2009). For example, attending to a specific sensory signal is thought to enhance the precision of the predictions related to that signal, subsequently influencing associated prediction errors (Hohwy, 2012). Consistent with the characterisation of the HEP as a neural correlate of precision-weighted interoceptive prediction error, many studies have reported attentional modulation of the amplitude of the HEP – for example, during tasks involving attending to heartbeat sensations relative to external stimuli (García-Cordero et al., 2017; Montoya et al., 1993; Petzschner et al., 2019; Schandry et al., 1986; Villena-González et al., 2017; Yuan et al., 2007).

The relative weight of precision in perceptual inference is also influenced by individual differences in relative uncertainty (Lawson et al., 2014; Seth & Friston, 2016). For example, individuals who are accurate at identifying when sounds are synchronous with their heartbeat (i.e. performance on the heartbeat detection task) also exhibit higher HEP amplitudes relative to individuals who are poor heartbeat perceivers, just as in an attentive versus inattentive contrast (Katkin et al., 1991; Pollatos et al., 2005; Pollatos & Schandry, 2004; Schandry et al., 1986). Indeed, Ainley et al. (2016) have previously characterised these individual differences in interoceptive ability as individual differences in relative precision of prediction errors. However, caution should be taken when interpreting differences across interoceptive ability groups, as multiple heartbeat detection paradigms exist, which assess distinct processes and may not measure interoceptive ability validly (Brener & Ring, 2016; Corneille et al., 2020; Ring & Brener, 2018). In addition, Garfinkel et al. (2015) suggested three distinct and dissociable dimensions of interoceptive ability: interoceptive sensibility, accuracy, and awareness, with each dimension potentially influencing predictive mechanisms differently (Garfinkel et al., 2015).

Consequently, a combined study of attention to interoceptive signals and individual differences in interoceptive ability allows us to directly test this predictive framework within the domain of evoked potentials. Specifically, here we report the effect of attention and interoceptive ability on interoceptive predictions reflected in the electrical potentials evoked by omissions within a heartbeat detection task. As omission-evoked responses reflect top-down predictions from higher cortical regions, our approach allows us to measure the influence of attentional precision on interoceptive prediction and error signals, without contaminating bottom-up input (Chennu et al., 2016; Wacongne et al., 2011). Consistent with characterisations of the precision-weighting nature of both within-subject and between-subject variations in attention (Chennu et al., 2016; Feldman & Friston, 2010b; Hohwy, 2012), we hypothesised that HEPs during auditory omission periods would be 1) larger when sounds are perceived as synchronous with the heartbeat, 2) larger when the heartbeat is attended, and 3) larger for those individuals with high interoceptive ability. At the source level, we anticipated increased anterior insula activation when sounds are perceived as synchronous, supporting the role of the insula as a hub for interoceptive and exteroceptive integration (Gray et al., 2007; Salomon et al., 2016). Furthermore, we hypothesised increased activation in the insula, cingulate cortex, and somatosensory cortex (postcentral gyrus) when directing attention internally, than externally, and in individuals with high interoceptive perception, than poor interoceptive perceivers, as previously observed in fMRI studies (Critchley et al., 2004; García-Cordero et al., 2017).

2.3 Materials and Methods

Unless otherwise stated, all methods, analyses, and hypotheses were pre-registered at [https://osf.io/nr8my/].

2.3.1 Participants

We recruited 39 participants from the University of Birmingham via advertisement on posters or the online SONA Research Participation Scheme. Our inclusion criteria were: right-handed 18 to 35-year-olds, with no reported cardiovascular or neurological disorders. We compensated participants with course credit. The Psychology Research Ethics Board of the University of Birmingham granted ethical approval for this study and written informed consent was completed by all participants. The data of five participants were excluded because of poor data quality resulting in more than a third of the trials of interest rejected. Subsequent analyses were completed on a final sample of 34 participants (Median age = 20 years, Range = 18-28 years). We chose this sample size in advance as it provides 80% power to detect a medium effect size (0.5) in our within-subjects interaction between attention and cardio-audio delay (alpha=.05; GPower, Faul et al., 2007).

2.3.2 Stimuli and Procedure

The experiment consisted of four blocks of 56 trials (224 trials total), with each trial consisting of 7 to 10 auditory tones (1000Hz, 100ms duration, 44100 sampling rate) presented via external speakers, with breaks given between each block. The onset of each tone was triggered by the online detection of the participants R-peak from electrocardiography (ECG) recordings using Lab Streaming Layer and a custom MATLAB script (Kothe et al., 2018). The script analysed in real time the raw ECG signal by computing the variance over the preceding 33ms window and determining if the signal exceeded an individually adjusted threshold, at which point a tone was triggered to occur after either an average time of 287ms (perceived synchronous) or 587ms (perceived asynchronous) delay (Brener & Kluvitse, 1988a; Wiens & Palmer, 2001). Due to computational variability in online detection of R-peaks, R->Sound intervals had a standard deviation of 30ms for both the perceived synchronous and asynchronous trials. In half of the trials, the third from last tone was omitted, resulting in an R-peak without an auditory stimulus. A fixation cross was present during tone presentation.

A cue at the start of each trial (200ms) directed participants' attention to focus internally ('Heart') or externally ('Tone'). During the internal task, participants focused on their heartbeat sensations (without taking their pulse), and determined whether the tones presented were synchronous or not with their heartbeat. During the external task, participants were told to ignore their heartbeat sensations and direct attention towards the sounds alone. The external task was to determine whether there was a missing sound during that trial. Participants responded to the internal task ('Were The Tones Synchronous With Your Heart?') or external task

(‘Was There a Missing Tone?’) question by pressing ‘y’ for yes or ‘n’ for no on the keyboard, and rated their confidence in their decision from 1 to 4 (1 = total guess, 2 = somewhat confident, 3 = Fairly Confident, 4 = Complete Confidence). The inter-trial interval was between 2 to 3 seconds, chosen from a uniform distribution on each trial (see Figure 4). The order of the experimental conditions were randomized to ensure no more than 3 of the same condition on consecutive trials. Finally, participants completed the short Porges Body Perception Questionnaire (BPQ), including a body awareness and autonomic reactivity subscale (Porges, 1993).

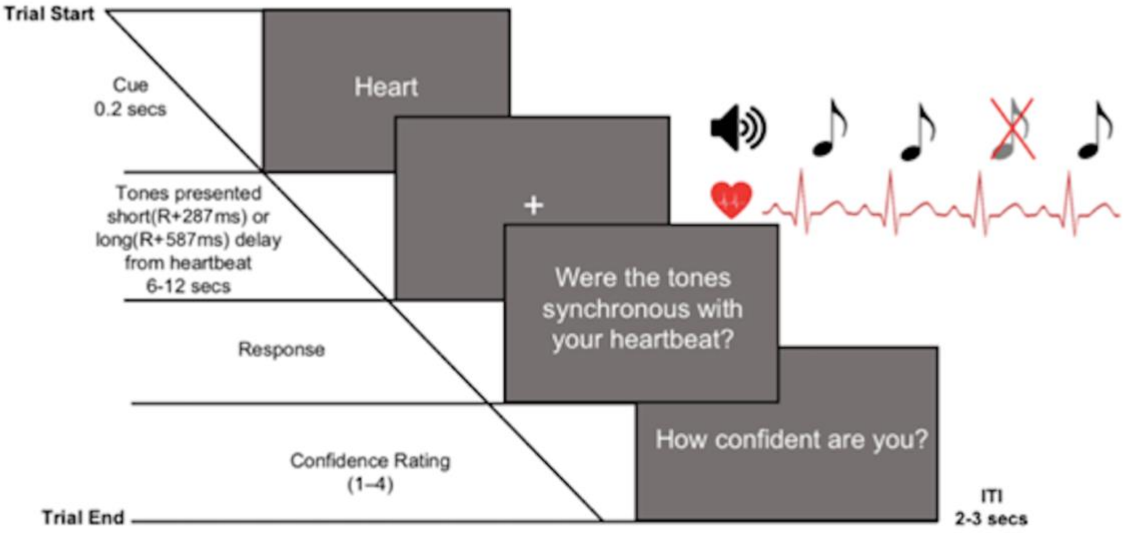

Figure 4. Experimental design of the integrated heartbeat detection (internal attention) and omission detection task (external attention), displaying an internal attention trial.

2.3.3 Indices

Interoceptive accuracy was calculated by comparing the normalised proportion of hits (responding ‘yes’ to a short cardio-audio delay ‘R+287ms’ trial) with the normalised proportion of false alarms (responding ‘yes’ to a long cardio-audio delay ‘R+587ms’ trial) (i.e. internal task d-prime *(d’)*) (Macmillan & Creelman, 1990). Additionally, we calculated exteroceptive accuracy by comparing the normalised proportion of hits (responding ‘yes’ to a trial including an omission) with the normalised proportion of false alarms (responding ‘yes’ to a trial without an omission) (external task *d’*). The proportion of hits and false alarms were normalised using the inverse of the standard normal cumulative distribution.

As in previous studies (Ewing et al., 2017; Garfinkel et al., 2015), we quantified sensibility to a variety of internal bodily sensations with the score on the awareness subsection of the Porges Body Perception Questionnaire (BPQ) (Porges, 1993) and defined sensibility to heartbeat sensations as the median confidence rating during internal trials (Ewing et al., 2017; Forkmann et al., 2016; Garfinkel et al., 2015).

Interoceptive awareness was calculated using type 2 signal detection theory analysis comparing observed type 2 sensitivity (meta-*d'*) with expected type 2 sensitivity (*d'*) (Maniscalco & Lau, 2012). Meta-*d'* is the *d'* expected to generate the observed type 2 hit rates and type 2 false alarm rates and was estimated using maximum likelihood estimation (MLE) (Maniscalco & Lau, 2014). This determined the extent to which confidence ratings predicted heartbeat detection accuracy, and thus interoceptive awareness. Groups were separated into high/low interoceptive accuracy, sensibility, and awareness with median splits.

2.3.4 EEG/ECG acquisition

EEG was recorded throughout the experiment using a gel-based 128-channel Biosemi ActiveTwo system, acquired at 512Hz, referenced to the Common Mode Sense electrode located approximately 2-cm to the left of CPz. Two additional electrodes recorded data from the mastoids, and ECG was measured using two electrodes placed on either side of the chest, also sampled at 512Hz.

2.3.5 EEG/ECG Pre-Processing

First, we filtered the continuous EEG data in two steps (i.e. high-pass then low-pass) between 0.5Hz and 40Hz using the finite impulse response filter implemented in EEGLAB (function: pop_eegfiltnew). We filtered ECG between 0.5Hz and 150Hz (Kligfield et al., 2007). Next, we segmented the filtered EEG signals into epochs from -300ms to 800ms relative to the R-peak of the ECG recording during the omission period, re-referenced to the average of the mastoids. We detected the R-peaks using a custom MATLAB script, and subsequently checked the accuracy of R-peak detection via visual inspection. When necessary, we manually corrected the estimated R-peaks to ensure accurate R-peak detection. To account for online heartbeat detection errors (i.e. missed or multiple sounds per R-peak), we rejected blocks with R-R intervals > 1.5 seconds or < 0.4 seconds from both behavioural and EEG analyses. The subsequent artefact rejection proceeded in the following steps based on a combination of methods described by Nolan et al., 2010 and Mognon et al., 2011 (Mognon et al., 2011; Nolan et al., 2010).

First, bad channels were identified and removed from the data. We consider a channel to be bad if its absolute z-score across channels exceeds 3 on any of the following metrics: 1) variance of the EEG signal across all time-points, 2) mean of the correlations between the channel in question and all other channels, and 3) the Hurst exponent of the EEG signal (estimated with the discrete second order derivative from the Matlab function *wfbmesti*). After removal of bad channels, we identified and removed trials containing non-stationary artefacts. Specifically, we considered a trial to be bad if its absolute z-score across trials exceeds 3 on any of the following metrics: 1) the mean across channels of the voltage range within the trial, 2) the mean across channels of the variance of the voltages within the trial, and 3) the mean across channels of the difference between the mean voltage at that channel in the trial in question and the mean voltage at that channel across all trials. After removal of these individual trials, we conducted an additional check for bad channels, and removed them, by interrogating the average of the channels across all trials (i.e. the evoked response potential (ERP), averaged across all conditions). Specifically, we considered a channel to be bad in this step if its absolute z-score across channels exceeds 3 on any of the following metrics: 1) the variance of voltages across time within the ERP, 2) the median gradient of the signal across time within the ERP, and 3) the range of voltages across time within the ERP.

To remove stationary artefacts, such as blinks and eye-movements, the pruned EEG data is subjected to independent component analysis with the *runica* function of EEGLAB. The Matlab toolbox ADJUST subsequently identified which components reflect artefacts on the basis of their exhibiting the stereotypical spatio-temporal patterns associated with blinks, eye-movements, and data discontinuities, and the contribution of these artefact components is then subtracted from the data (Mognon et al., 2011). Next, we interpolated the data of any previously removed channels via the spherical interpolation method of EEGLAB, and re-referenced the data to the average of the whole head.

We included an additional preprocessing step beyond those planned in our pre-registration to control for differences in the cardiac field artefact (CFA) at our different delay conditions (Nakamura & Shibasaki, 1987). Specifically, we calculated single-subject average HEPs during rest periods, following the same preprocessing pipeline as the experimental HEPs. In a similar approach to that used in previous research (van Elk et al., 2014), we then subtracted the average resting HEP from individual experimental trials, locked to each heartbeat. This conservative method eliminates remaining artefacts due to additional heartbeats within the same trial.

Before proceeding to group-level analyses, single-subject CFA-corrected averages for HEP analysis are finalised in the following way. First, a robust average was generated for each condition separately, using the default parameters of SPM12. Robust averaging iteratively down-weights outlier values by time-point to improve estimation of the mean across trials. As recommended by SPM12, the resulting HEP was low-pass filtered below 20Hz (again, with

EEGLAB's pop_neweegfilt). In a deviation from our pre-registration, but following discussions with peer reviewers and investigation of similar decisions in previous studies of HEPs (Azzalini et al., 2019; Babo-Rebelo et al., 2016, 2019; Park et al., 2014a), we chose not to apply any baseline correction to our data as cardiac activity is cyclical by nature and may therefore insert artefactual effects in post-R data.

2.3.6 HEP Analysis

HEPs during the omission period were compared with the cluster mass method of the open-source Matlab toolbox FieldTrip (fieldtrip-20181023) (Oostenveld et al., 2011). This procedure involves an initial parametric step followed by a non-parametric control of multiple-comparisons (Maris & Oostenveld, 2007). Specifically, we conducted either two-tailed dependent samples t-tests (for comparison 1) or a combination of two-tailed independent and dependent samples t-tests (for comparison 2) at each spatio-temporal data-point within the time window. Spatiotemporally adjacent t-values with p-values < 0.05 are then clustered based on their proximity, with the requirement that a cluster must span more than one time-point and at least 4 neighbouring electrodes, with an electrode's neighbourhood containing all electrodes within a distance of .15 within the Fieldtrip layout coordinates (median number of neighbours = 11, range 2-16). Finally, we summed the t-values at each spatio-temporal point within each cluster. Next, we estimated the probability under the null hypothesis of observing cluster sum Ts more extreme than those in the experimental data - i.e. the p-value of each cluster. Specifically, Fieldtrip randomly shuffles the trial labels between conditions, performs the above spatio-temporal clustering procedure, and retains the largest cluster sum T. Consequently, the p-value of each cluster observed in the data is the proportion of the largest clusters observed across 1000 such randomisations that contain larger cluster sum T's.

Our pre-registered analyses were to be conducted on the ERP data from 100ms to 600ms relative to the R-peak. However, it subsequently became evident that this approach is confounded by the lag difference in tone presentation across conditions. Consequently, here we report one set of analyses on ERP data from 0ms to 229ms post-R (i.e. the first percentile of the short delay R-sound intervals, thus before 99% of anticipated tones) and a second set of analyses from 0ms to 213ms relative to the onset of the omitted sound (i.e. from 287ms to 500ms post-R for the short delay condition, and 587ms to 800ms post-R for the long delay condition).

2.3.7 Comparisons

Using the above method, HEPs were compared across cardio-audio delay and attention conditions to assess the main effects, and the interaction was calculated as the difference between short-delay and long-delay trials between attention groups (i.e. a double-subtraction; comparison 1). If an interaction was observed, pairwise separate analyses were completed to consider simple effects. Similar comparisons were completed across attention and interoceptive individual difference conditions (interoceptive awareness, accuracy and sensibility) (comparison 2).

2.3.8 CFA Control Analyses

We performed control analyses on the ECG data, to determine if differences in cardiac activity contributed towards the HEP results. Therefore, equivalent analyses to that performed on the HEPs were completed on the ECG data. Subsequently, single-subject robust averages of the ECG activity were computed for each condition and were analysed using the cluster mass method, as described above. The same comparisons were completed as to those which showed a significant HEP effect (i.e. ECG was compared across cardio-audio delay conditions 0-229ms post-R, and the attention and delay interaction was assessed 0-213ms relative to the omission).

2.3.9 HEP Control Analyses

As our analyses involved comparing HEPs at different latencies relative to the R-peak, it is possible that artefactual effects could be inserted due to the relative position of the underlying HEP, rather than due to differing cognitive processes. To test this concern, we performed the same analyses on HEPs recorded prior to the onset of any sounds in the trial – i.e. before any task-related processing could become evident. Specifically, single-subject robust averages of pre-sound HEP activity relative to the first R-peak after the cue were computed for each condition and analysed using the cluster mass method, and using the same comparisons as those which showed significant HEP effects (cardio-audio delay conditions were compared 0-229ms post-R, and the attention and delay interaction was assessed using the same window as the omission-locked analysis (i.e. from 287ms to 500ms post-R for the short delay condition, and 587ms to 800ms post-R for the long delay condition)).

To further control for residual HEP differences and reinforce our main effect of delay, we analysed the difference between delay conditions before the first and fourth sound. We chose the fourth sound as the omission could occur from the fifth sound onward. Therefore, robust averages were computed relative to the R-peak for the first and fourth sound. We averaged pre-sound HEP activity belonging to the electrodes and time-window of the significant pre-omission positive and negative clusters separately, for each participant. Subsequently, a two-way ANOVA analysed the interaction of cardio-audio delay (short and long delay) and sound number (first and fourth sound) and post-hoc t-tests analysed the effect of cardio-audio delay separately for the first and fourth sound.

2.3.10 Source Reconstruction

Since our initial pre-registration, we discovered that our planned source analysis pipeline performed poorly at localising basic sensory responses in a separate study in our lab. Consequently, we concluded that those pre-registered methods were inappropriate for this study. Therefore, here we report a more rudimentary but validated source reconstruction method, using statistical parametric mapping (SPM12) (Henson et al., 2009; López et al., 2014).

Our source estimation approach was completed for each time-window separately in which we observed a significant sensor level effect: 27-230ms post-R for the main effect of delay, 95-138ms relative to the omission for the attention and delay interaction (i.e. 382-425ms post-R for the short delay condition and 682-725ms post-R for the long delay condition), and 102-138ms relative to the omission for the follow-up simple effects analysis (i.e. difference between cardio-audio delay conditions for internal and external trials separately: 389-425ms post-R for the short delay condition and 689-725ms for the long delay condition). We note that the selection of time-windows for source estimation are not orthogonal to the sensor level effects, however source estimation only assisted with the qualitative interpretation of the sensor level effects (i.e., no source statistics were performed). For each time-window, within SPM12, we applied a hanning taper to downweight the signal at the beginning and end of the window in the condition-wise grand averages, and filtered the data between 1 and 48 Hz. Cortical sources of each sensor-level HEP were reconstructed using the default anatomical template in SPM. Electrode positions were co-registered to the template using the fiducials of the nasion, left peri-auricular and right peri-auricular points. We calculated the forward model using the Boundary Element Method. The inverse model was generated based on an empirical Bayesian approach. Specifically, we applied the greedy search fitting algorithm, which optimises the multiple sparse priors approach when localising the sensor-level evoked responses. Finally, we contrasted the condition-wise source estimates (i.e. generated difference source volumes). The estimated source results were projected onto a canonical inflated brain surface for visualisation, using the open source MNI2FS toolbox (Price., 2020 : https://github.com/dprice80/mni2fs).

2.4 Results

2.4.1 Behavioural data

Participants' interoceptive accuracy scores (internal *d'*) were significantly greater than zero (M=0.218, SD=0.347; t(33) = 3.665, *p* < .001, BF_{10} = 36.52). This indicates that performance on the heartbeat discrimination task was above chance and therefore confirms our interpretation of the R+287ms cardio-audio delay as perceived synchronous and R+587ms as perceived asynchronous. Additionally, performance on the external task (external *d'*) was significantly greater than zero (M=3.091, SD=1.105; t(33) = 3.665, *p* < .001, BF_{10} = 2.273e+14), indicating that participants were attentive during both tasks.

Table 1. *Median (and range) of interoceptive ability dimensions: interoceptive accuracy (i.e., d' prime during internal trials), interoceptive awareness (i.e., meta d' prime), and three measures of interoceptive sensibility (body awareness subscale (BPQ_BA) and autonomous nervous system reactivity subscale (BPQ_ANS) of the Porges Body Perception Questionnaire, as well as confidence ratings during internal trials). High and low interoceptive ability groups created via median splits.*

Interoceptive accuracy (d' prime)	Interoceptive awareness (meta-d)	Interoceptive sensibility (BPQ_BA)	Interoceptive sensibility (BPQ_ANS)	Interoceptive sensibility (confidence)
0.204 (-0.447-1.274)	-0.269 (-1.134-0.782)	58 (42-126)	29 (20-47)	3 (1.5-4)

There was no significant difference in exteroceptive performance between the short delay (M=2.943, SD=1.056) and long delay trials (M=2.990, SD=0.938) (t(33) = -.470, *p* = .642). A Bayesian equivalent analysis indicated the data were 5x (1/.204) more likely to occur under a model with no effect of cardio-audio delay (BF_{10} = .204), demonstrating that external task performance is likely to be independent from heartbeat perception. Also, there was no significant correlation between internal and external task accuracy, further suggesting that performance on the internal and external task was independent (r(32) = .299, *p* = .085, BF_{10} = .883).

2.4.2 Heart-evoked potentials

2.4.2.1 Cardio-audio expectation

We observed a significant early dipolar main effect of cardio-audio delay (positive cluster *p* = .001, and negative cluster *p* = .005), perhaps reflecting a difference in expectation induced by the heartbeat. Estimated generators of this effect include bilateral primary somatosensory cortex, bilateral primary motor cortex, bilateral supramarginal gryus, right anterior prefrontal cortex, and bilateral middle temporal cortex. The positive cluster extended from 27-230ms and the negative cluster 93-169ms post R-peak, with the cardio-audio delay conditions reflected in qualitatively different topographic distributions, supporting our hypothesis of the role of cardiac signals to predict auditory stimuli. We observed no significant main effect of attention on pre-omission responses (smallest cluster *p* = .062) (see Figure 5).

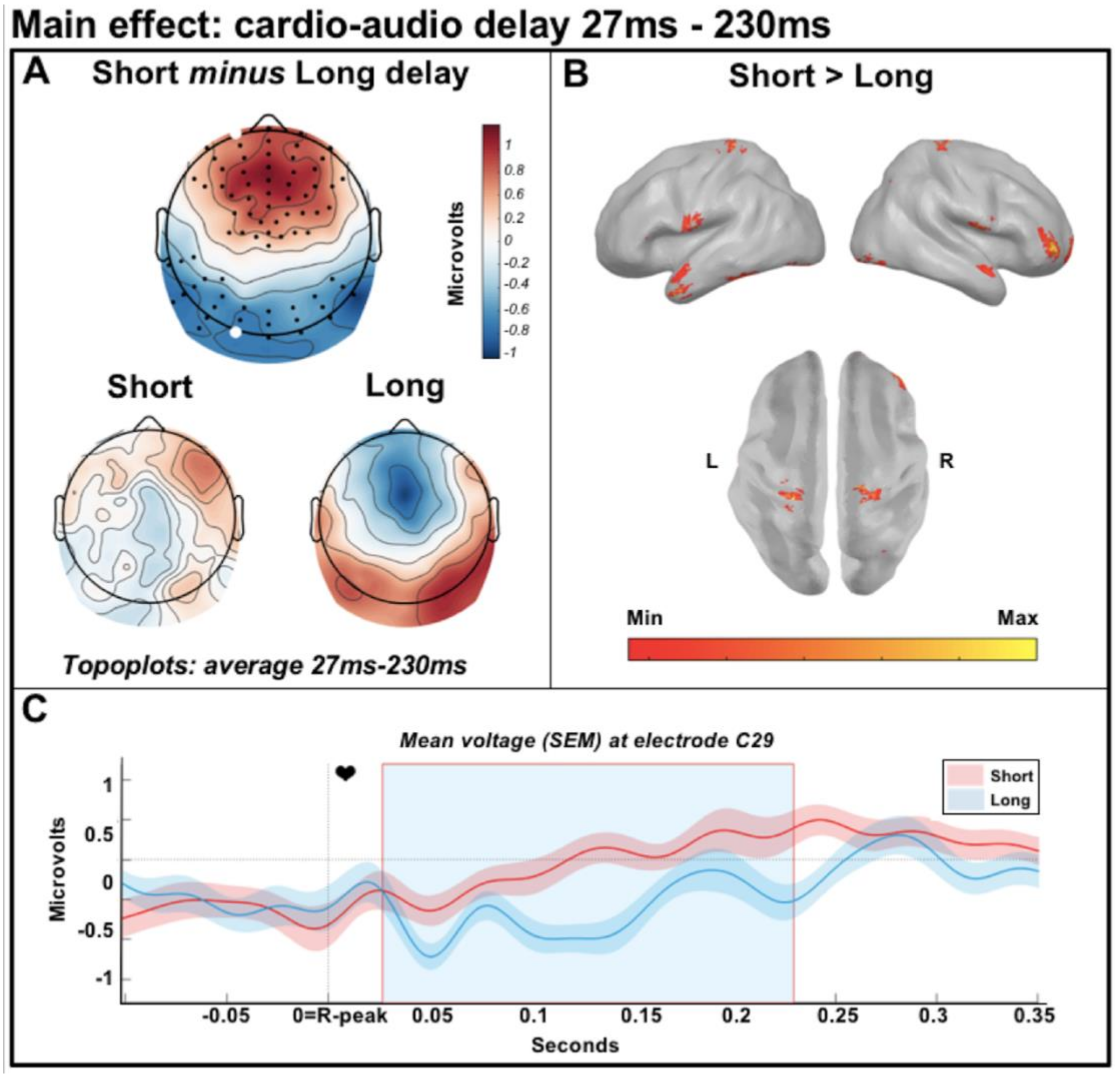

Figure 5. *Main effect of cardio-audio delay from 27ms-230ms, reflecting differences in cardio-audio expectation. [A] Scalp distribution of the average significant difference across delay conditions 27-230ms, with electrodes contributing to the dipolar clusters marked. [B] Estimated sources of the main effect in bilateral primary somatosensory cortex, bilateral primary motor cortex, bilateral supramarginal gyrus, right anterior prefrontal cortex and bilateral middle temporal cortex. [C] Average HEP across participants at electrode C29, light blue shaded region represents the time of the significant positive effect. Note, no baseline correction was performed to avoid the insertion of differences which reflect the processing of the previous heartbeat or preparatory cardiac commands, however, with baseline correction the polarity of results may differ.*

2.4.2.2 Unfulfilled expectation

The cluster-based permutation test indicated a significant, though weak, interaction between cardio-audio delay and attention (cluster p = .017) with estimated sources in right inferior frontal gyrus, bilateral supramarginal gyrus and right middle temporal cortex, supporting our hypothesis of attentional modulation of predictive mechanisms. The cluster in the observed data extended from 95-138ms post omission. Follow-up simple effects tests indicated a larger positivity within this cluster for short-delay omissions relative to long-delay omissions during internal attention only (cluster extended 102-138ms, *p* = .007), while there were no clusters formed when contrasting the cardio-audio delay conditions when externally attending. This supports our hypothesis of larger HEPs during omission periods within short delay (perceived synchronous) than long delay (perceived asynchronous) trials. Source analyses estimated internal simple effects in bilateral supramarginal gyrus, right inferior frontal gyrus, bilateral orbitalfrontal cortex, bilateral anterior prefrontal cortex and bilateral middle and superior temporal cortex, while external simple effects were estimated in bilateral angular gyrus, left supramarginal gyrus, left premotor cortex, bilateral anterior prefrontal cortex, left fusiform gyrus, and bilateral temporopolar area (see Figure 6).

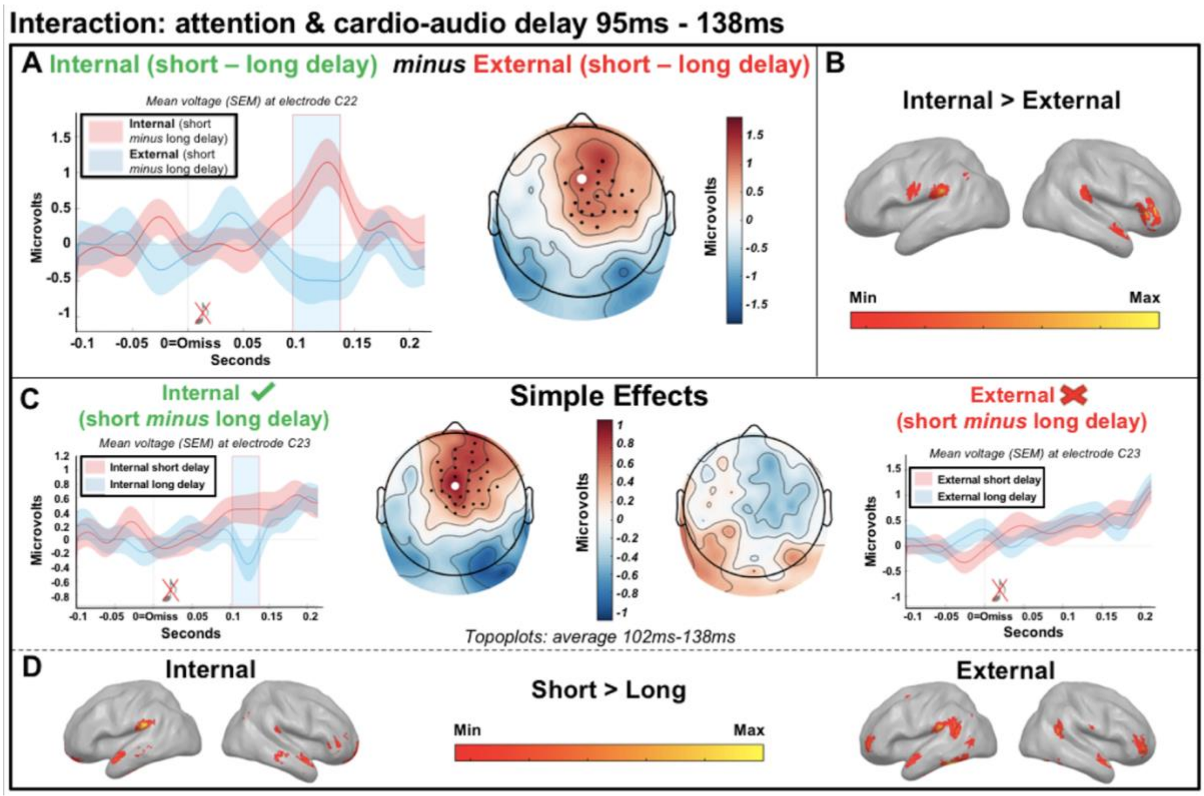

Figure 6. Interaction between attention and cardio-audio delay from 95ms-138ms, relative to the omitted sound. [A - left] Average omission evoked response across participants at electrode C22, light blue shaded region represents the time of the significant effect. [A - right] Scalp distribution of the average significant interaction (attention x delay) 95ms-138ms, with electrodes contributing to the cluster marked. [B] Estimated sources of the interaction in the right inferior frontal gyrus, bilateral supramarginal gyrus and right middle temporal cortex. [C] Analysis of the simple effects showing qualitatively different topographical distributions across attention conditions (102ms-138ms), and a significant effect of delay in the internal attention condition only. [D - left] Estimated sources of internal simple effects analysis in bilateral supramarginal gyrus, right inferior frontal gyrus and bilateral orbitalfrontal cortex, bilateral anterior prefrontal cortex and bilateral middle and superior temporal cortex. [D - right] Estimated sources of external simple effects analysis in left premotor cortex, bilateral angular gyrus, left supramarginal gyrus, bilateral anterior prefrontal cortex, left fusiform gyrus, and bilateral temporopolar area. Note, no baseline correction was performed to avoid the insertion of differences which reflect the processing of the previous heartbeat or preparatory cardiac commands, however, with baseline correction the polarity of results may differ.

2.4.2.3 Control ECG comparisons

We observed no difference clusters when comparing ECG responses between cardio-audio delay conditions, 0-229ms post-R. Similarly, no clusters were found when analysing the interaction between attention and cardio-audio delay on ECG responses, 0-213ms relative to the omitted sound. Therefore, we conclude that it is unlikely that ECG activity contributed towards the HEP differences observed.

2.4.2.4 Interoceptive ability

Cluster-based permutation tests indicated no significant interaction of high and low interoceptive awareness (smallest *p* = .388), accuracy (smallest *p* = .231) or sensibility (both median confidence rating and the awareness subsection of the BPQ; smallest *p* = .138) with attention, during short delay trials.

We also completed exploratory correlations of interoceptive ability with the amplitude of each participant's delay effect during the interaction time window (95ms-138ms relative to the omission). These analyses reveal no significant correlation between the delay effect and interoceptive accuracy (*r*(32) = -.004, p = .984, BF$_{10}$ = .213) or interoceptive awareness (*r*(32) = .007, *p* = .968, BF$_{10}$ = 0.214) during external attention, or the delay effect and interoceptive accuracy (*r*(32) = -.156, *p* = .377, BF$_{10}$ = 0.310) or awareness (*r*(32) = -.000, *p* = .998, BF$_{10}$ = 0.213) during internal attention (see Figure 7). Additionally, no significant correlations were found with interoceptive sensibility (both the awareness subsection score and the autonomic reactivity subsection score of the BPQ) (smallest *p* = .300) for both internal and external trials. Additionally, there was no significant equivalent correlations during the main effect of delay time window (27-230ms relative to the R-peak) (smallest *p* = .162). This is inconsistent with our hypothesis of interoceptive ability modulating predictive responses.

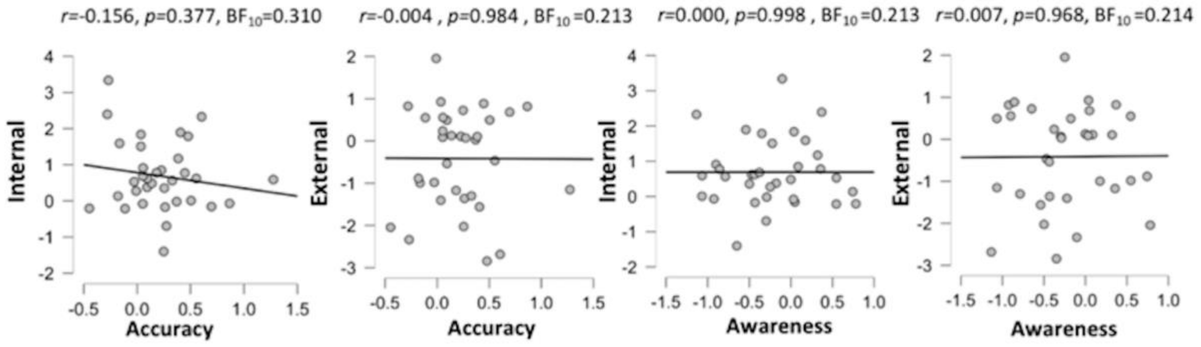

Figure 7. Correlations of interoceptive accuracy and interoceptive awareness with the mean difference in voltage across cardio-audio delay conditions during the significant interaction window for internal and external trials.

2.4.2.5 HEP Control Analyses

2.4.2.5.1 Cardio-audio expectation

We would predict that a true expectation effect (as we interpret our pre-omission effect to be) would be evident in the R->Sound periods of all sounds in that trial, perhaps increasing in magnitude over the trial as more evidence accumulates about whether the trial is short or long delay. Therefore, we analysed the main effect of delay before the fourth sound and compared this with the delay effect before the first sound of each trial, using the significant electrodes and time-window of the positive and negative pre-omission clusters. This analysis indicated a significant interaction between trial position and delay (positive cluster: F(1,33) = 5.447, p = 0.026, partial n^2 = 0.142; negative cluster: F(1,33) = 6.022, p = 0.020, partial n^2 = 0.154), indicating a greater difference between the delay conditions before the fourth sound (positive difference=0.460; negative difference=0.641) than before the first sound (positive difference=0.243, negative difference=0.211), consistent with our view that the pre-omission effect reflects an expectation that has built-up across the trial.

However, follow up t-tests indicated a significant differences between the delay conditions for both the first sound (positive cluster: t(33) = 3.598, p =.001; negative cluster: t(33) = -2.469, p =.019) and the fourth sound (positive cluster: t(33) = 8.526, p <.001; negative cluster: t(33) = -6.530, p <.001). Topographically, the delay effect before the fourth sound is very similar to that we observe before the omission, whereas the delay effect before the first sound has a qualitatively distinct topography, indicative of not entirely overlapping cognitive processes or neural generators (see Supplementary Figure 17).

2.4.2.5.2 Unfulfilled expectation

As the omission-locked analyses involved analysing HEPs at different moments (R+287ms for the short delay condition and R+587ms for the long delay condition), it is possible that our effect could be due to comparing early and late HEP components, irrespective of cardio-audio integration. To control for this, we analysed the attention and delay interaction using the same time-windows (R+287ms and R+587ms) relative to the first R-peak post cue (before any sounds) and found no significant interaction (p =.609). Therefore, we interpret this control analysis as evidence that the omission-locked attention and delay interaction is not a result of comparing HEPs at different moments post-R.

2.4.3 Interbeat intervals (IBIs)

Because previous research found differences in the interbeat intervals following omissions and deviant stimuli, we additionally investigated this as an exploratory analysis (Pfeiffer & De Lucia, 2017; Raimondo et al., 2017). IBIs were significantly longer during internal attention (M=834.356ms, SD=108.000ms) than during external attention (M=813.442ms, SD=102.074ms; F(1,33) = 69.475, *p* <.001, partial n^2 = .678, $BF_{inclusion}$ = 3.002e+15). However, there was no significant IBI difference between the cardio-audio delay conditions (F(1,33) =

2.342, *p* =.135, partial n^2 =.066, BF$_{inclusion}$ = .484), nor was there a significant interaction between attention and cardio-audio delay (F(1,33) = 3.223, *p* =.082, partial n^2 =.089, BF$_{inclusion}$ = .479).

Additionally, we calculated the IBI's relative to the omission, revealing an IBI increase post-omission when attending externally. A three-way ANOVA analysed the IBIs post-omission (IBI 'omission to 1' and IBI '1 to 2') across cardio-audio delay and attention conditions (see Figure 8). This revealed a main effect of IBI (F(1,33) = 17.320, *p* <.001, partial n^2 = .344, BF$_{inclusion}$ = 7.739), a main effect of attention (F(1,33) = 25.391, *p* <.001, partial n^2 = .435, BF$_{inclusion}$ = 1.481e+10), a main effect of delay (F(1,33) = 4.605, *p* =.039, partial n^2 = .122, BF$_{inclusion}$ = 6.579), a significant delay and attention interaction (F(1,33) = 5.062, *p* =.031, partial n^2 = .133, BF$_{inclusion}$ = 9.945) and a significant attention and IBI interaction (F(1,33) = 13.717, *p* <.001, partial n^2 = .294, BF$_{inclusion}$ = 2.819). The delay and IBI interaction was not significant (F(1,33) = .339, *p* =.565, partial n^2 = .010, BF$_{inclusion}$ = .471), and the delay, attention and IBI interaction was not significant (F(1,33) = .007, *p* =.932, partial n^2 <.001, BF$_{inclusion}$ = .329) (see Figure 8).

Posthoc t-tests revealed that the first IBI after the omission (IBI omission to 1) was significantly faster (short delay: M=818.674, SD=106.089; long delay: M=807.908, SD=96.939) than the following IBI (IBI 1 to 2) (short delay: M=830.529, SD=107.646; long delay: M=818.255, SD=100.182) for external attention trials during both cardio-audio short delay stimulation (t(33) = -4.820, *p* <.001, BF$_{10}$ = 726.098) and long delay stimulation (t(33) = -3.535, *p* =.001, BF$_{10}$ = 26.644). There was no significant difference between the post-omission IBIs during internal attention trials ((short delay: t(33) = -.981, *p* =.334, BF$_{10}$ = .286); (long delay: W = 234, *p* =.285, BF$_{10}$ = .187)). This appears to reflect a cardiac deceleration when the omission was a target (i.e. during external attention) (see Figure 8).

Posthoc t-tests also revealed a significant IBI difference between the cardio-audio delay trials during external attention (IBI omiss to 1: t(33) = 2.640, *p* =.013, BF$_{10}$ = 3.559; IBI 1 to 2: W = 442, *p* =.012, BF$_{10}$ = 1.764), whereas there was no significant IBI difference between cardio-audio delay trials during internal attention (IBI omiss to 1: t(33) = -.474, *p* =.639, BF$_{10}$ = .204; IBI 1 to 2: t(33) = .082, *p* =.935, BF$_{10}$ = .184).

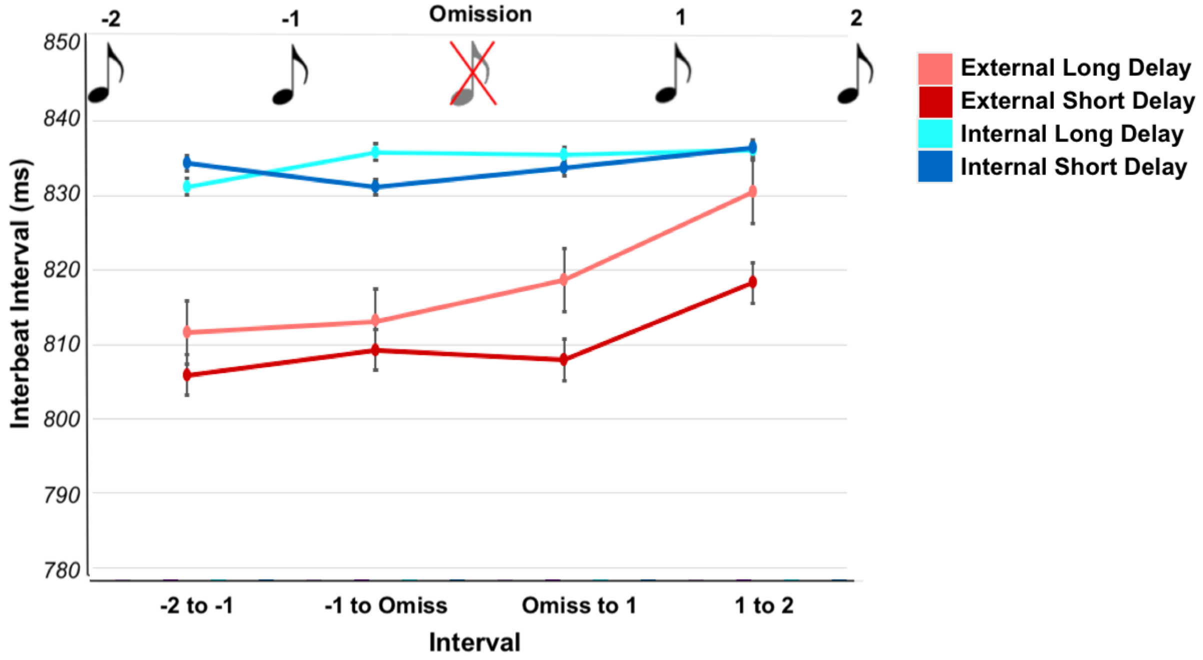

Figure 8. Interbeat intervals in relation to the omission, with error bars reflecting standard error.

2.4.4 Heart rate variability

We analysed the standard deviation of the IBI's (SDRR) as a measure of heart rate variability (HRV). A two-way ANOVA on the SDRR values revealed that the IBI's was significantly more variable when internally attending (short delay: M=77.18, SD=20.81; long delay: M=78.64, SD=25.96) than when externally attending (short delay: M=73.07, SD=21.94, long delay: M=76.32 SD= 26.65) ($F(1,33) = 5.481$, $p = .025$, $n^2 = .142$). However, a Bayesian equivalent analysis revealed only weak evidence of an effect of attention on HRV ($BF_{inclusion}$ = 1.361). While there was no significant interaction between attention and delay ($F(1,33) = .546$, $p = .465$, $n^2 = .016$, $BF_{inclusion}$ = .295), the HRV difference between delay conditions was larger when externally attending (difference = 3.25) than when internally attending (difference = 1.46). As these effects are in the opposite direction to those reported in the HEPs, we conclude that the HRV task differences are unrelated to our HEP effects. Finally, there was no significant main effect of cardio-audio delay ($F(1,33) = 2.135$, $p = .153$, $n^2 = .061$, $BF_{inclusion}$ = .497).

2.5 Discussion

Several theories propose that emotion and embodied self-awareness arise from the integration of internal and external signals and their respective precision-weighted expectations (Barrett & Simmons, 2015; Seth, 2013; Seth et al., 2012; Seth & Friston, 2016). Here we investigated these mechanisms of integrated interoceptive and exteroceptive expectations by comparing HEPs during heartbeat-predicted omissions, thus allowing a measure of pure prediction signals without the contamination of bottom-up auditory inputs (Chennu et al., 2016; Wacongne et al., 2011).

First, we observed a pre-omission HEP difference when comparing cardio-audio delay trials, reflected in qualitatively different topographical distributions (see Figure 5A). Consistent with the hypothesis that interoceptive signals guide expectations of exteroceptive stimuli, this result indicates that different expectations of upcoming sounds are induced by different cardio-audio delays, and that these differential expectations are supported by not entirely overlapping regions of cortex. Pfeiffer & De Lucia (2017) reported a similar HEP difference during omission periods when comparing cardio-audio synchronous stimulation with asynchronous stimulation, supporting the integration of cardiac signals to predict auditory stimuli. However, because the sounds in that study (and therefore omission responses) were time-locked to the R-peak during synchronous stimulation but shuffled relative to the R-peak in the asynchronous condition, the auditory omission response is confounded in that contrast. We control for this in our study by comparing trials with sounds at fixed cardio-audio intervals, ensuring the auditory omission response is time-locked to the heartbeat in both delay conditions. This allows for the comparison of pre-omission periods, and later omission-locked responses, which subsequently excludes the auditory omission response as a confound. Nevertheless, our HEP differences across perceived synchrony are consistent with that reported by Pfeiffer & De Lucia (2017). Similarly, in another study consistent with heartbeat-driven auditory predictions, van Elk et al., (2014) observed a weak auditory N1 suppression to heartbeat-locked sounds, in comparison to cardio-audio asynchronous sounds, although not statistically significant in that study (p = .07).

As further evidence that the pre-omission effect of delay reflects differential expectations, we also observed that this effect increases in magnitude across the trial, perhaps as evidence accumulates regarding the short/long delay nature of the trial. Nevertheless, we also observe a significant effect of delay in the period before the first sound of the trials – i.e. before any expectation could be formed – with a qualitatively distinct topography indicative of distinct processes and generators to the effect we observe later in the trial and pre-omission. While this result does not affect our interpretation of the pre-omission expectation effect, as the effects across the trial are clearly electrophysiologically distinct, it highlights the possibility for significant HEP effects to be generated by factors not related to the task. Consequently, considerable control analyses are required in studies of HEPs to moderate cognitive interpretations (discussed further below).

We also observe an interaction between attention and cardio-audio delay when comparing omission-locked evoked responses. This is present as a larger positivity to short delay omissions than long delay omissions, when attending internally only. This supports our hypothesis of stronger unfulfilled expectations of a tone in trials presenting sounds at a short perceived synchronous delay than at a longer perceived asynchronous delay. These results are additionally consistent with the role of top-down attentionally-mediated mechanisms in generating expectations of upcoming stimuli. This is supported by modelling evidence, highlighting that omissions are generated by top-down driving inputs, which are attentionally modulated via strengthened downward connections (Chennu et al., 2016). Source estimates of the attentionally mediated omission-locked response revealed the orbitofrontal cortex and inferior frontal gyrus during internal attention only, while the anterior prefrontal cortex and supramarginal gyrus was consistently implicated in all cardio-audio delay contrasts (i.e. during the R-locked main effect of delay (see Figure 5B) and the omission-locked internal and external simples effects (see Figure 6D), suggesting that the prediction of a sound in relation to the heartbeat may originate from these areas. This is broadly consistent with previous cardiac attention research which highlight the prefrontal cortex, although usually the inferior or middle frontal gyrus (Critchley et al., 2004; Kuehn et al., 2016; Pollatos et al., 2007; S. M. Schulz, 2016; Simmons et al., 2013; Wiebking et al., 2010; Zaki et al., 2012). Additionally, the supramarginal gyrus has previously been implicated during a variety of interoceptive attention/awareness tasks and is thought to be related to the multisensory integration of information from the body and the environment (Kashkouli Nejad et al., 2015; Reichenbach et al., 2011; Salvato et al., 2020).

Previous research indicated that attention enhances mismatch and omission responses, further supporting the role of attention at modulating predictive mechanisms (Chennu et al., 2013, 2016; Garrido et al., 2009; Raij et al., 1997). Despite this, Pfeiffer & De Lucia (2017) reported a heart-beat driven prediction error effect in a group of participants who were naive to the presence of omissions, contrary to our results of absent heartbeat-driven effects when not attending to the heartbeat. Nevertheless, our observation that attention did not modulate the magnitude of our pre-omission HEP effect but did modulate the amplitude of the omission-locked ERP effect is consistent with a view that the expectation of an upcoming sound can be instantiated without direct attention, but that attention differentially enhances the precision of those expectations so that their violations (i.e. omissions) lead to ERP effects that are modulated by attention (Kok et al., 2012).

The modulating nature of attention on HEPs is consistent with previous research and with the interpretation of the HEP as a marker of precision-weighted prediction error of each individual heartbeat (García-Cordero et al., 2017; Montoya et al., 1993; Petzschner et al., 2019;

Schandry et al., 1986; Villena-González et al., 2017; Yuan et al., 2007). Attention is proposed to modulate predictive mechanisms by enhancing the precision of attended prediction errors, relative to the precision of their priors (Ainley et al., 2016; Hohwy, 2012; Petzschner et al., 2019). Subsequently, attending to internal signals could enhance the precision of interoceptive prediction errors, resulting in their propagation up the predictive hierarchy to update models for more accurate future predictions regarding each heartbeat. The enhanced cardiac predictions would in turn allow for more precise auditory predictions of heartbeat-locked sounds, such as those presented in our task. Therefore, the enhanced predictions of each heartbeat due to internal attention allow for more precise priors regarding the timing of sounds relative to those heartbeats. The larger positivity to short-delay omissions may be because heartbeat-driven predictions of external stimuli are only stable/accurate across relatively short intervals from the heartbeat (i.e. ~287ms). Similarly, Critchley et al., (2004) found a greater difference in fMRI activity between cardio-audio delay conditions when attending internally, than externally. This was reflected as an increase in the frontal operculum and insula, dorsal and medial parietal lobe, right dorsolateral prefrontal cortex, dorsal cingulate, and lateral temporal cortices during internal attention relative to external. This cortical network overlaps broadly with the source estimates of our interaction of attention with cardio-audio delay in the right inferior frontal gyrus, bilateral supramarginal gyrus, and middle temporal cortex.

As individual differences in the ability to perceive heartbeat sensations can also be framed as differences in precision, we expected interoceptive accuracy and awareness to similarly modulate interoceptive predictive mechanisms. However, we found no relationship between interoceptive ability and the HEP differences observed in our task. The lack of evidence for a relationship between our ERP effects and participants' interoceptive abilities during internal attention is inconsistent with previous evidence that interoceptive accuracy modulated HEP responses (Katkin et al., 1991; Pollatos et al., 2005; Pollatos & Schandry, 2004; Schandry et al., 1986). However, previous research used heartbeat counting tasks to assess interoceptive performance, rather than the heartbeat discrimination task used in our study, which likely confounds ability to estimate heart rate or time with the ability to sense individual heartbeats (Brener & Ring, 2016; Corneille et al., 2020; Ring & Brener, 2018). The lack of observed differences between interoceptive ability groups in our study could also be because of individual differences in the timing of heartbeat sensations, likely due to biological differences (Wiens & Palmer, 2001). Therefore, some individuals may have performed poorly because they perceived both delay conditions as asynchronous (Brener et al., 1993b; Brener & Ring, 2016). This could be investigated in future research by previously determining each individual's perceived synchronous delay (using the method of constant stimuli (Brener et al., 1993b), for example) and subsequently individually adjusting the ‘perceived synchronous’ cardio-audio delay used for each individual (Brener & Kluvitse, 1988a; Mesas & Chica, 2003). It is also possible that HEP differences related to interoceptive ability occur at later latencies than we could measure in our design. For example, ERPs related to metacognition are thought to occur at late latencies (between 550-1900ms) which would overlap with ERPs evoked by successive auditory stimuli in our design (Skavhaug et al., 2010; Sommer et al., 1995; Tsalas et al., 2018). Furthermore, interoceptive metacognitive awareness has previously been associated with long-range connectivity patterns (global activity), rather than HEP local activity differences (Canales-Johnson et al., 2015). Future investigation of these connectivity markers in our data may reveal further relationships.

A potential limitation of our task design is that the internal and external tasks differ in their difficulty. However, we argue that if our observed HEP differences are the result of a task difficulty confound then we would expect that these effects would also correlate with interoceptive performance, which they do not. A further potential limitation is that the omission is task-relevant in the external task only, perhaps reflected in the post-omission cardiac deceleration during external trials. The task-relevance of the omission in the external condition may have directed participants attention directly to the prediction error signal, potentially modulating precision differently than in the internal condition. However, we do not observe any HEP differences as a result of cardio-audio delay during external attention, which would not be expected if task relevance of the omission were an influence on the predictive effects reflected in the HEP. Future research could use an alternative external task of increased difficulty with equal omission task-relevance, such as determining the synchronicity of sounds with a faint flashing visual stimulus, excluding task-related differences as a potential confound. Additionally, the tasks may have differed in the temporal scale used to make each decision, with the external task perhaps requiring a longer time-period of integration to correctly identify omitted sounds relative to the time-period of integration required to judge cardio-audio synchronicity. However, the precise periods of temporal integration and their electrophysiological effects across tasks are unclear without further future quantification.

Previous research has stressed the importance of controlling for ECG artefacts when comparing HEP responses (Kern et al., 2013; van Elk et al., 2014). We corrected for ECG artefacts using a similar method to that used by van Elk et al (2014), by subtracting the average HEP response during rest periods for each participant. Our correction was potentially more conservative as it was time locked to each heartbeat within individual trials. Considering the ECG correction applied, the lack of heart rate or heart rate variability differences in the direction of the ERP effects and the lack of statistical difference between ECG responses across conditions of interest, we conclude that our observed HEP differences are unlikely to be due to differences in ECG activity, but rather reflect predictive mechanisms of the integration of internal and external stimuli. Another potential confound is a consequence of comparing different moments of the HEP (i.e. R+287ms vs R+587ms). Thus, one could argue that the observed omission-locked interaction may simply reflect different components of the underlying HEP. However, our control analysis indicated no evidence of a significant interaction when applying the same analyses to HEP data before presentation of any sounds, thus strengthening our cognitive interpretation of this effect.

Our results support the mechanisms underlying interoceptive predictive coding accounts that suggest that embodied selfhood and emotional experience are a result of integrated self-related predictions from multiple modalities (including interoceptive, exteroceptive and proprioceptive signals) (Barrett & Simmons, 2015; Seth, 2013; Seth et al., 2012; Seth & Friston, 2016). This is supported by studies which demonstrated the contribution of integrative interoceptive signals with visual cues to enhance body ownership and self-recognition (Aspell et al., 2013; Heydrich et al., 2018; Sel et al., 2017; Suzuki et al., 2013). Additionally, interoceptive and exteroceptive integration has been suggested to explain the generation of a first-person perspective, describing how our unified conscious experience of the external world is integrated with the experience of the self, with particular focus on interoception as a binding agent (Azzalini et al., 2019). These viewpoints, therefore, demonstrate the potential function of the integrated interoceptive and exteroceptive mechanisms observed in our study.

Investigating HEP differences across cardio-audio delay conditions may be a useful clinical tool for assessing dysfunctional interoceptive-exteroceptive predictive mechanisms. As mentioned, the experience of emotion or selfhood is proposed to be the result of the integration of interoceptive predictive mechanisms with exteroception and proprioception (Seth & Friston, 2016). Therefore, measuring pure predictive signals during omissions, which reflect interoceptive and exteroceptive integration, may be useful for diagnosing dissociative disorders, schizophrenia, or anxiety (Paulus & Stein, 2006; Petzschner et al., 2019; Seth, 2013; Seth et al., 2012; Synofzik et al., 2010). Additionally, if interoceptive and exteroceptive integrative mechanisms contribute towards a unified conscious first-person perspective, then observing preserved mechanisms could be useful for diagnosing awareness in patients with disorders of consciousness (Azzalini et al., 2019). This would be advantageous because current methods of assessing awareness focus almost exclusively on responses to external stimuli, whereas assessing interoceptive and exteroceptive integration could provide a method of assessing both external perceptual and internal self-related aspects of awareness.

In conclusion, our results demonstrate that interoceptive signals can guide expectations of exteroceptive stimuli and that attentional-precision modulates integrative cross-modal predictive mechanisms. Nevertheless, we found no evidence that the HEPs were related to subjective experience of heartbeat sensations suggesting low validity of our two-alternative-forced-choice method of assessing interoceptive awareness, or that there exists a more subtle interaction of HEPs and subjective experience. The integrative interoceptive and exteroceptive predictive mechanisms described here provide a useful tool for assessing embodied and interoceptive predictive coding accounts of cognition and clinical disorders.

CHAPTER 3: IMPROVED INVESTIGATION OF TRAIT PRECISION VIA INDIVIDUALLY-TAILORED TIMING OF HEARTBEAT PERCEPTION[2]

3.1 Abstract

Interoceptive-exteroceptive integration is fundamental for a unified interactive experience of the world with the body. Predictive coding accounts propose that these integrated signals operate predictively, with regulation by precision-weighting. Heartbeat-evoked potentials (HEPs) are one means to investigate integrated processing. In a previous study, consistent with predictive coding characterisations of precision-weighting, we observed modulation of HEPs by attention. However, we found no evidence of HEP modulation by participants' interoceptive ability, despite the characterisation by predictive coding theories of trait abilities as a similar reflection of differential precision-weighting. In this study, we sought to more sensitively test the hypothesised trait precision influences on HEPs by using an individually-adjusted measure of interoceptive performance. However, contrary to a precision-weighted predictive coding framework, we failed to find evidence in support of the HEP modulations by attentional-precision or trait precision. Nonetheless, we observed robust HEP effects indicative of an expectation of a sound on the basis of a heartbeat –i.e. interoceptive-exteroceptive integration. It is possible that under our more individually-tailored task, participants relied less on attentional-precision to 'boost' predictions due to an enhanced perception of cardio-audio synchrony. Furthermore, assessing interoceptive ability is challenging, thus variations in performance may not accurately reflect trait precision variations. Nevertheless, in sum, our findings are inconsistent with a precision-weighted prediction error view of the HEP, and highlight the need for clearer definitions of the manipulation and measurement of precision in predictive coding. Finally, our robust interoceptive-exteroceptive integration HEP effects may provide a valuable tool for investigating such integration in both clinical conditions and cognition.

Key words:

Heart-evoked potentials, interoceptive-exteroceptive integration, predictive coding, precision, expectation.

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[2] As published in:
Banellis, L., & Cruse, D. (2021). Heartbeat-evoked potentials during interoceptive-exteroceptive integration are not consistent with precision-weighting. *bioRxiv*. https://doi.org/10.1101/2021.02.03.429610 (Includes slight differences due to PhD corrections).

3.2 Introduction

Predictive coding accounts describe the brain as probabilistically inferring the causes of upcoming sensory events (Friston, 2010; Rao & Ballard, 1999). Under these accounts, predictions from generative models are compared with inputted sensory information, with the discrepancy computed as prediction error. Predictive mechanisms are accomplished hierarchically, with predictions feeding into each layer top-down, and prediction errors bottom-up. The predictive coding framework is linked to many aspects of cognition, perception, and action, with 'successful' processes resulting from the minimisation of prediction error across all levels of the hierarchy (Enns & Lleras, 2008; Wolpert & Flanagan, 2001; Kilner et al., 2007; DeLong et al., 2005; Frith & Frith, 2006; Clark, 2013; Friston, 2010).

Although initially applied to exteroceptive processing, it became apparent that for the framework to encompass the integrated experience of perceiving and interacting with the world via the body, inferences of both internal and external systems must be intertwined (Allen & Friston, 2018; Friston, 2009; Petzschner et al., 2017; Pezzulo, 2014; Seth & Friston, 2016). Thus, predictive coding models emerged that encompassed the inferential processing of the body – specifically, interoceptive signals reflecting visceral bodily sensations and internal bodily states (Barrett & Simmons, 2015; Cameron, 2002; Seth, 2013; Seth et al., 2012; Seth & Friston, 2016; Sherrington, 1952).

One method of measuring cortical interoceptive processing is via heartbeat-evoked potentials (HEPs) – averaged neural electrophysiological signals time-locked to heartbeats (Park & Blanke, 2019; Pollatos & Schandry, 2004). Although discovered more than 30 years ago (Schandry et al., 1986), the study of HEPs is still in its infancy, with debate over the appropriate pre-processing/analysis methods, and controls for correcting confounds such as the cardiac field artefact (CFA) (Coll et al., 2021; Park & Blanke, 2019). This may in part explain the diverse spatial and temporal observation of the HEP across the literature. However, it is likely that the HEP reflects contributions from multiple sources, including baroreceptors, cardiac afferents, cutaneous receptor somatosensory mapping, and neuro-vascular coupling (Park & Blanke, 2019).

HEPs are primarily recorded from superficial pyramidal neurons via M/EEG (i.e. the proposed location of prediction error units), therefore some have interpreted HEP amplitude to reflect precision-weighted prediction error of each heartbeat (Ainley et al., 2016; Petzschner et al., 2019). Precision is the weight given to predictions and subsequent errors, reflected by the inverse of the variance, or the uncertainty. Attention is thought to increase the precision of the prediction errors of the attended sensory channel via synaptic gain control, enhancing model updating (Friston, 2009; Hohwy, 2012). Consistent with the role of attentional precision in modulating predictive mechanisms, previous research demonstrated attentional modulation of HEPs, supporting its interpretation as a precision-weighted prediction error signal (Banellis & Cruse, 2020; Mai et al., 2018; Montoya et al., 1993; Petzschner et al., 2019; Villena-González et al., 2017; Yuan et al., 2007).

Trait variations in uncertainty, such as individual differences in the ability to accurately sense the heartbeat, are proposed to similarly modulate predictive mechanisms via precision-weighting. For example, those with high heartbeat detection performance demonstrate larger HEP amplitudes than low heartbeat perceivers, comparable to internal/external attention contrasts (Katkin et al., 1991; Pollatos et al., 2005; Pollatos & Schandry, 2004; Schandry et al., 1986). However, on the surface, this result appears at odds with a prediction error interpretation as one might expect largest HEPs in circumstances of highest error, i.e., for low heartbeat perceivers. This disparity is often reconciled via appeal to precision-weighting, such that a small prediction error weighted by high precision may result in a larger evoked potential than a large prediction error weighted by low precision (Kok et al., 2012). However, care should be taken when interpreting trait variations as different heartbeat detection tasks assess distinct processes and some tasks may not validly measure ability (Brener & Ring, 2016; Corneille et al., 2020; Desmedt et al., 2020; Ring & Brener, 2018).

The cross-modal predictive mechanisms proposed to underlie an integrated experience of perceiving the world via the body can be investigated by presenting exteroceptive stimuli at different intervals from the heartbeat. For example, tones presented at short delays from the heartbeat (~250ms) are typically perceived as synchronous, while those presented at longer delays (~550ms) are typically perceived as asynchronous with the heart. Furthermore, when participants listen to sequences of such synchronous or asynchronous sounds, we previously observed an HEP effect in the period between the heartbeat and the expected sound, potentially reflecting cardio-audio integrated expectations (Banellis & Cruse, 2020). In support of attentional modulation of integrated predictive mechanisms, we also observed a larger positivity to unexpectedly omitted sounds in a sequence of cardio-audio synchronous sounds *only* when participants were attending to their heartbeat.

However, in that same study we found no evidence of evoked potential modulation by participants' trait heartbeat perception abilities, thus failing to support the hypothesised trait precision contribution to HEPs (Katkin et al., 1991; Pollatos et al., 2005; Pollatos & Schandry, 2004; Schandry et al., 1986). One potential cause of this lack of evidence is that we failed to account for individual differences in the temporal location of heartbeat sensations (Brener & Ring, 2016). Multi-interval tasks, such as the Method of Constant Stimuli (MCS), are more sensitive at determining interoceptive ability as the optimal relative timing of heartbeat sensations is not presumed (Brener et al., 1993a; Brener & Ring, 2016). For example, higher accuracy in a two-interval task can be achieved by first determining the optimal timing of each individual's heartbeat sensations in a multi-interval task (Brener & Kluvitse., 1988a/b; Mesas & Chica., 2003).

Therefore, in this study, we sought to more sensitively test for trait precision influences on HEPs using the above method of individually-adjusted timings. Furthermore, we sought to replicate our previously observed effects of attention and cross-modal expectations on HEPs. Together, this study tests the hypotheses of predictive coding theories that HEPs reflect precision-weighted predictive mechanisms, where precision can be defined as both attentional gain and trait ability.

3.3 Materials and Methods

Unless otherwise stated, all methods, analyses, and hypotheses were pre-registered at [https://osf.io/ptbzf/]

3.3.1 Participants

Forty participants were recruited from the University of Birmingham via advertisement on posters or the online SONA Research Participation Scheme. Our inclusion criteria included: right-handed 18 to 35-year olds, with no reported cardiovascular or neurological disorders. We compensated participants with course credit or payment at a rate of £10 an hour. The STEM Research Ethics Board of the University of Birmingham granted ethical approval for this study and written informed consent was completed by all participants. Data of six participants were excluded due to EEG recording difficulties or poor data quality, resulting in more than a third of trials of interest rejected. One participant was rejected from part one (due to insufficient trials) but included in part two of the EEG analysis (and the opposite for a different participant). A final sample of 34 participants were included for both parts of subsequent EEG analyses (Median age = 20 years, Range = 18-35 years). This sample size was chosen in advance, as it provides 95% power to detect the same effect size (Cohen's d' = 0.58) as the within-subjects interaction between attention and cardio-audio delay observed in our previous experiment (preregistered analysis: M=0.0349, SD=0.0598; alpha=.05; note that the effect size in the final published version of that study [Banellis & Cruse., 2020] was slightly larger [0.61] due to pre-processing changes suggested by peer reviewers; GPower, (Faul et al., 2007)).

3.3.2 Stimuli and Procedure

3.3.2.1 Overview

The experiment consisted of two parts; the function of part one was to determine the temporal location of perceived heartbeat sensations for each individual, using the Method of Constant Stimuli (MCS) (Brener et al., 1993a; Brener & Kluvitse, 1988a; Ring & Brener, 2018; Schneider et al., 1998). Part two comprised of a variant of a two-interval forced choice heartbeat discrimination task, with individually adjusted perceived synchronous and perceived asynchronous cardio-audio delays calculated from the median of their linearly interpolated cumulative distribution of choices from the MCS task (Brener & Kluvitse, 1988a, Brener & Kluvitse, 1988b; Mesas & Chica, 2003). Additionally, part two included an attention manipulation and interoceptive ability measurements, allowing the investigation of the effects of precision on cross-modal predictive mechanisms.

3.3.2.2 Part one: Method of constant stimuli

Part one consisted of three blocks of 40 trials (120 trials total), with each trial consisting of 5 to 7 auditory tones (1000Hz, 100ms duration, 44100 sampling rate) presented via external speakers, with breaks given between each block. The onset of each tone was triggered by the online detection of the participants R-peak from electrocardiography (ECG) recordings using Lab Streaming Layer and a custom MATLAB script (Kothe et al., 2018). The script analysed in real time the raw ECG signal by computing the variance over the preceding 33ms window and determining if the signal exceeded an individually adjusted threshold, at which point a tone was triggered to occur after one of six cardio-audio delays (an average time of 113ms, 213ms, 314ms, 413ms, 510ms, or 612ms delay). Due to computational variability in online detection of R-peaks, R->Sound intervals had a standard deviation of between 24ms-26ms. A fixation cross was present during tone presentation.

Participants focused on their heartbeat (without taking their pulse) and determined whether the tones presented were synchronous or not with their heartbeat. At the end of each trial, participants responded to the question ‘Were the tones synchronous with your heart?’ by pressing ‘y’ for yes or ‘n’ for no on the keyboard. The inter-trial interval was between 2 to 3 seconds, chosen from a uniform distribution on each trial (see Figure 9). The order of the experimental conditions was randomized to ensure no more than 3 of the same condition on consecutive trials.

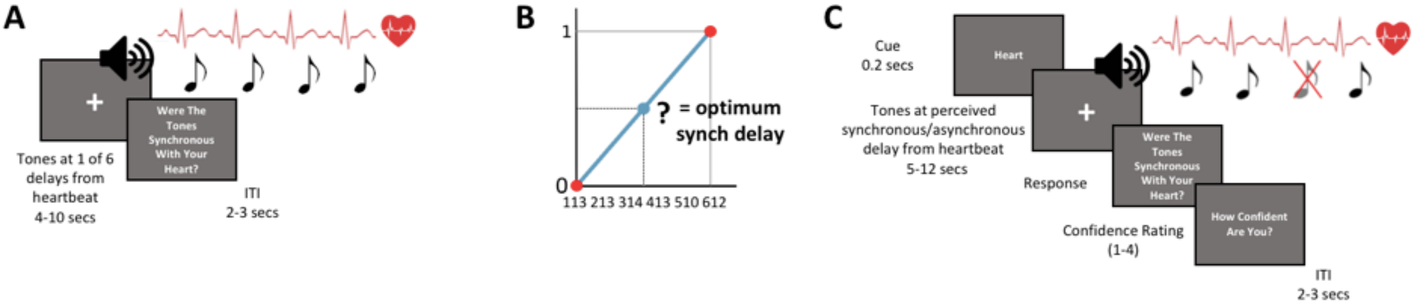


Figure 9. (A) Part 1 of the experiment consisted of a multi-interval heartbeat discrimination task (MCS) in which sounds were presented at 1 of 6 intervals from the heartbeat (113ms, 213ms, 314ms, 413ms, 510ms, or 612ms). (B) Calculation of each individuals perceived synchronous delay from the median of the linearly interpolated cumulative distribution of choices from the MCS task (marked as the question mark). (C) Part 2 of the experiment consisted of an individually adjusted two-interval heartbeat discrimination task for half of the trials (internal attention; as shown in C), and half consisted of an omission-detection task (external attention).

3.3.2.3 Part two: Individually-adjusted two-interval task

Part two consisted of three blocks of 56 trials (168 trials total), with each trial consisting of 7 to 10 auditory tones triggered by the online detection of the participant's R-peak (as above in part one), presented via external speakers, with breaks given between each block. We selected each individual's perceived synchronous cardio-audio delay from their performance in part one (i.e. the MCS), by calculating the median from the linearly interpolated cumulative percentage sum of their response counts for each delay (Brener & Kluvitse, 1988a, Brener & Kluvitse, 1988b; Mesas & Chica, 2003), and we selected the perceived asynchronous delay to be 300ms later (SD= 0.001) than the perceived synchronous delay, as in Mesas and Chica (2003). Due to computational variability in the online detection of R-peaks, R->Sound intervals had a standard deviation of 45ms for both the perceived synchronous and asynchronous trials. In half of the trials, we omitted the third from last tone, resulting in an R-peak without an auditory stimulus – an omission. We presented a fixation cross during tone presentation.

A cue at the start of each trial (200ms) directed participants' attention to focus internally ('Heart') or externally ('Tone'). During the internal task, participants focused on their heartbeat sensations (without taking their pulse) and determined whether the tones presented were synchronous or not with their heartbeat. During the external task, participants were told to ignore their heartbeat sensations and direct attention towards the sounds alone. The external task was to determine whether there was a missing sound during that trial. After each task response, participants rated their confidence in their decision from 1 to 4 (1 = Total Guess, 2 =

Somewhat Confident, 3 = Fairly Confident, 4 = Complete Confidence). The inter-trial interval was between 2 to 3 seconds, chosen from a uniform distribution on each trial (see Figure 9). We randomized the order of the experimental conditions to ensure no more than 3 of the same condition on consecutive trials. Finally, participants completed the short Porges Body Perception Questionnaire (BPQ), including a body awareness and autonomic reactivity subscale (Porges, 1993).

3.3.2.4 EEG/ECG acquisition

We recorded EEG throughout the experiment using a gel-based 128-channel Biosemi ActiveTwo system, acquired at 512Hz, referenced to the Common Mode Sense electrode located approximately 2-cm to the left of CPz. Two additional electrodes recorded data from the mastoids, and ECG was measured using two electrodes placed on either side of the chest, also sampled at 512Hz.

3.3.2.5 EEG/ECG Pre-Processing

First, we filtered the continuous EEG data in two steps (i.e. low-pass then high pass) between 0.5Hz and 40Hz using the finite impulse response filter implemented in EEGLAB (function: pop_eegfiltnew). We filtered ECG between 0.5Hz and 150Hz (Kligfield et al., 2007) and in addition to that preregistered, we notch-filtered the ECG between 48Hz and 52Hz to remove line noise. Next, we segmented the filtered EEG signals into epochs from -300ms to 900ms relative to the R-peak of the ECG recording during within-task omission periods. In addition to that preregistered, we segmented EEG data during silent periods at the end of trials without an omission as equivalent to a within-task omission, to increase power. End-trial silences are comparable to within-task omissions because participants could not predict when the trial would end due to the variable number of sounds in each trial. We segmented auditory-evoked potentials (AEPs) from -500ms to 500ms relative to the sounds during the MCS task and segmented HEPs -300 to 900ms relative to the first R-peak during end trial silent periods of the MCS task.

Initially, we re-referenced EEG data to the average of the mastoids. We detected the R-peaks using a custom MATLAB script, and subsequently checked the accuracy of R-peak detection via visual inspection. When necessary, we manually corrected the estimated timing of R-peaks to ensure accurate R-peak detection. To account for online heartbeat detection errors (i.e. missed or multiple sounds per R-peak), we rejected blocks with R-R intervals > 1.5 seconds or < 0.4 seconds from both behavioural and EEG analyses. In addition to that preregistered, to avoid contaminating responses within the analysis window, we rejected trials with triggers within 100ms prior to ERP onset (i.e., contaminating sounds for HEP trials and heartbeats for AEP trials).

For AEPs this included the rejection of trials with R-peaks within the analysis window (sound-500ms). The subsequent artefact rejection proceeded in the following steps based on a combination of methods described by Mognon et al., 2011 and Nolan et al., 2010.

First, bad channels were identified and removed from the data. We consider a channel to be bad if its absolute z-score across channels exceeds 3 on any of the following metrics: 1) variance of the EEG signal across all time-points, 2) mean of the correlations between the channel in question and all other channels, and 3) the Hurst exponent of the EEG signal (estimated with the discrete second order derivative from the Matlab function *wfbmesti*). After removal of bad channels, we identified and removed trials containing non-stationary artefacts. Specifically, we considered a trial to be bad if its absolute z-score across trials exceeds 3 on any of the following metrics: 1) the mean across channels of the voltage range within the trial, 2) the mean across channels of the variance of the voltages within the trial, and 3) the mean across channels of the difference between the mean voltage at that channel in the trial in question and the mean voltage at that channel across all trials. After removal of these individual trials, we conducted an additional check for bad channels, and removed them, by interrogating the average of the channels across all trials (i.e. the evoked response potential (ERP), averaged across all conditions). Specifically, we considered a channel to be bad in this step if its absolute z-score across channels exceeds 3 on any of the following metrics: 1) the variance of voltages across time within the ERP, 2) the median gradient of the signal across time within the ERP, and 3) the range of voltages across time within the ERP.

To remove stationary artefacts, such as blinks and eye-movements, the pruned EEG data is subjected to independent component analysis (ICA) with the *runica* function of EEGLAB. The Matlab toolbox ADJUST subsequently identified which components reflect artefacts on the basis of their exhibiting the stereotypical spatio-temporal patterns associated with blinks, eye-movements, and data discontinuities, and the contribution of these artefact components is then subtracted from the data (Mognon et al., 2011). Next, we interpolated the data of any previously removed channels via the spherical interpolation method of EEGLAB, and re-referenced the data to the average of the whole head.

We subjected the data to a second round of ICA, to remove the CFA. This deviated from our preregistration, as ICA was deemed a more stringent CFA correction method than subtracting a rest template (see Supplementary Figure 18) and is the most frequently used CFA-correction method in the HEP literature (Coll et al., 2021a; Park & Blanke, 2019). First, for the ICA computation, we filtered the ECG between 0.5Hz and 40Hz to ensure equivalent filtering as the EEG data and segmented the data into smaller epochs (-200ms to 200ms) with respect to the R-peak. We completed ICA on the shorter epoched data using the runica function of fieldtrip. To prevent multiple components with identical or symmetrical topographies, we set the maximum number of components to the rank of the data after trials concatenated. To select CFA components, we computed the pairwise phase coherence (PPC) of each component with the ECG. We selected a component if its PPC exceeded three standard deviations above the mean PPC of all components within the 0-25Hz range. We completed this selection procedure iteratively until no more than three components were selected. After visual inspection to ensure non-neural components had been identified, we removed the selected components from the original -300ms-900ms pre-processed EEG data. Finally, we visually inspected the data before and after CFA-correction and if the CFA was not visually diminished, we completed the cardiac ICA procedure again with an increased maximum number of rejected components, up to a maximum of six. The median number of components rejected across participants was 3 (range = 1-6).

Before proceeding to group-level analyses, we finalised single-subject CFA-corrected averages for HEP analysis in the following way. First, we generated a robust average for each condition separately, using the default parameters of SPM12. Robust averaging iteratively down-weights outlier values by time-point to improve estimation of the mean across trials. As recommended by SPM12, we low-pass filtered the resulting HEP below 20Hz (again, with EEGLAB's pop_neweegfilt). In deviation from our pre-registration, but following discussions with peer reviewers and investigation of similar decisions in previous studies of HEPs (Azzalini et al., 2019; Babo-Rebelo et al., 2016, 2019; Banellis & Cruse, 2020; Park et al., 2014b; Petzschner et al., 2019), we chose not to apply any baseline correction to our data as cardiac activity is cyclical by nature and may therefore insert artefactual effects in post-R data. This decision also allows direct comparison with published results of Banellis and Cruse (2020).

Finally, we visually inspected averaged ERPs to ensure the automated artefact rejection procedure was successful. If excessively large voltages remained in the averaged ERP, we visually inspected individual trials to ensure that any remaining channels/trials with excessively large voltages were removed. Additionally, if oculomotor artefacts remained then we identified additional ICA components and removed them manually.

3.3.2.6 ERP analysis

We compared ERPs with the cluster mass method of the open-source Matlab toolbox FieldTrip (Oostenveld et al., 2011: fieldtrip-20181023). This procedure involves an initial parametric step followed by a non-parametric control of multiple-comparisons (Maris & Oostenveld, 2007). Specifically, we conducted either two-tailed dependent samples t-tests (part

1 AEPs, part 1 HEPs, and part 2 attention and delay comparisons, see Supplementary Table 3: comparisons 1, 2, 3 and 4) or a combination of two-tailed independent and dependent samples t-tests (part 2 delay and interoceptive ability, and part 2 attention and interoceptive ability comparisons, see Supplementary Table 3: comparisons 5 and 6) at each spatio-temporal data-point within time window of interest. We clustered spatiotemporally adjacent t-values with p-values < 0.05 based on their proximity, with the requirement that a cluster must span more than one time-point and at least 4 neighbouring electrodes, with an electrode's neighbourhood containing all electrodes within a distance of .15 within the Fieldtrip layout coordinates (median number of neighbours = 11, Range = 2-16). Finally, we summed the t-values at each spatio-temporal point within each cluster. Next, we estimated the probability under the null hypothesis of observing cluster sum Ts more extreme than those in the experimental data - i.e. the p-value of each cluster. Specifically, Fieldtrip randomly shuffles the trial labels between conditions, performs the above spatio-temporal clustering procedure, and retains the largest cluster sum T. Consequently, the p-value of each cluster observed in the data is the proportion of the largest clusters observed across 1000 such randomisations that contain larger cluster sum T's.

For the HEP analyses, to account for the lag difference in tone presentation across delay conditions, we completed one set of analyses on HEP data before omission onset relative to the R-peak (part 1: R+0-113ms post-R (i.e. earliest perceived synchronous cardio-audio delay); part 2: 0-129ms post-R (i.e. first percentile of the R->sound intervals for the participant with the earliest perceived synchronous delay, thus before >99% of anticipated tones) and a second set of analyses relative to the onset of the omitted sound (part 1: 0-250ms relative to the most rated and least rated synchronous delay time; part 2: 95-138ms post-omission (i.e. significant attention and delay interaction from Banellis & Cruse., 2020)). This allows the investigation of cardio-audio expectation and unfulfilled expectation mechanisms separately. The AEP analysis windows were determined by the global field power (GFP) and global mass dissimilarity (GMD) of the most and least rated synchronous conditions together (i.e. first three components preregistered: 0-74ms, 74-154ms, 154-209ms, fourth and fifth component exploratory: 209-289ms, 289-500ms). See Supplementary Table 3 for analysis details for all comparisons.

3.3.2.7 Control Analyses

We performed a myriad of control analyses. This included analyses on physiological data (ECG, interbeat intervals (IBI's), heart rate variability (HRV)), as well as additional analyses on EEG data (HEP control analyses and analytical controls such as baseline correction and CFA correction control analyses). For details of all control analyses and control results, see Supplementary Control Analyses section.

3.3.2.8 Interoceptive ability correlations

We defined *interoceptive accuracy* as the difference between the normalised proportion of hits and the normalised proportion of false alarms (i.e. internal task *d'*, see above) (Macmillan & Creelman, 1990). As in previous studies (Ewing et al., 2017; Garfinkel et al., 2015), we quantified *sensibility* to a variety of internal bodily sensations with the score on the awareness subsection of the Porges Body Perception Questionnaire (BPQ) (Porges, 1993) and defined *sensibility* to heartbeat sensations as the median confidence rating during internal trials (Ewing et al., 2017; Forkmann et al., 2016; Garfinkel et al., 2015). We also calculated *interoceptive awareness* using type 2 signal detection theory analysis comparing observed type 2 sensitivity (meta-*d'*) with expected type 2 sensitivity (*d'*) (i.e. meta-d' – d') (Maniscalco & Lau, 2012). Meta-*d'* is the *d'* expected to generate the observed type 2 hit rates and type 2 false alarm rates and was estimated using maximum likelihood estimation (MLE) (Maniscalco & Lau, 2014). This determined the extent to which confidence ratings predicted heartbeat detection accuracy, and thus interoceptive awareness.

We correlated interoceptive ability (awareness, accuracy) with the mean difference in voltage across cardio-audio delay conditions during internal trials, using the electrodes and time-windows that demonstrated a significant main effect of cardio-audio delay (79-128ms post-R, and 94-137ms post-omission). In addition to that preregistered, to explore all aspects of interoceptive ability, we applied the same correlations during external trials and assessed the relationship of the above effects with interoceptive sensibility (body awareness and autonomic reactivity BPQ subsection separately), resulting in a total of 16 correlations.

3.3.2.9 Source Reconstruction

In addition to the analyses preregistered, we performed source reconstruction to estimate the neural origin of each significant ERP effect using the open-source software Brainstorm, which implements a distributed dipoles fitting approach (Tadel et al., 2011). We completed our source estimation approach for each time-window separately in which we observed a significant sensor level effect. Specifically, within Brainstorm, we computed a forward model using the Symmetric Boundary Element Method (BEM) as implemented in OpenMEEG, based on the default MRI anatomy (ICBM152). We imported into Brainstorm each participant's pre-processed EEG data prior to robust averaging, grouped by each attention and delay pair condition. We used a standard 128 Biosemi electrode position file for all participants. We generated the inverse model based on a minimum-norm solution using the current density map measure and unconstrained orientations, with an equal noise covariance matrix. We computed a grand average of the source results for each condition and subsequently averaged across the time window of each significant sensor-level effect. We calculated the difference between source maps and subsequently computed the norm of the three orientations, thus reflecting changes in source amplitude and orientation but not sign between source maps. We projected the estimated source results onto a canonical inflated brain surface for visualisation (plotting parameters: local maximum, amplitude=70%, minimum cluster=5).

3.4 Results

3.4.1 Behavioural data

3.4.1.1 Part one: MCS performance

We calculated the percentage preference for each delay by dividing the simultaneous judgement counts (total 'yes' responses for each delay trial) by the total trials for each delay after the removal of faulty blocks (R-R intervals > 1.5 seconds or < 0.4 seconds, as described above). Across participants, the mean delay at which sounds were perceived synchronous with the heart was 295.686 (SD=39.081) (see Figure 10A). We classified a good heartbeat perceiver in part one on the basis of a Chi^2 test which determined if the distribution of each individual's simultaneous judgements deviated significantly from chance (see Figure 10B) (Ring & Brener, 2018). This revealed a significant Chi^2 effect for 8/34 participants for part 1 and part 2 each, and therefore defined 9 high heartbeat perceivers in total and 26 low heartbeat perceivers. (see Supplementary Table 6 for individual performance).

3.4.1.2 Part two: Internal performance

Interoceptive accuracy (internal task d-prime), calculated from hits (responding 'yes' to a short 'perceived synchronous' cardio-audio delay trial) and false alarms (responding 'yes' to a long 'perceived asynchronous' cardio-audio delay trial; Macmillan & Creelman, 1990), was significantly greater than zero on average across the group (Mdn=0.271, Range=-0.445-2.166; Z = 530, $p < .001$, $r_{rb} = 0.782$), indicating that the sounds presented at individually adjusted cardio-audio delays were successfully perceived as synchronous and asynchronous. However, a Bayesian equivalent analysis indicated the evidence was weak relative to the null ($BF_{10} = 2.876$).

To determine whether individually-adjusted cardio-audio delays improved heartbeat perception, we compared internal performance here with that reported in an equivalent previous experiment without individually-adjusted delays (Banellis & Cruse, 2020). While interoceptive accuracy was more variable and had a higher median in this experiment (Mdn=0.271, Range=-

0.445-2.166), than in the previous experiment with fixed delays (Mdn=0.204, Range=-0.447-1.274), this difference was not statistically significant (U = 502, *p* .134, r_{rb} = -0.156, BF_{10} = 0.463; note this remains non-significant with the removal of outliers) (see Figure 10C).

Table 2. *Median (and range) of interoceptive ability dimensions from the individually-adjusted two interval task: interoceptive accuracy (i.e., d' prime during internal trials), interoceptive awareness (i.e., meta d' prime), and three measures of interoceptive sensibility (body awareness subscale (BPQ_BA) and autonomous nervous system reactivity subscale (BPQ_ANS) of the Porges Body Perception Questionnaire, as well as confidence ratings during internal trials). High and low interoceptive ability groups created via median splits.*

Interoceptive accuracy (d' prime)	Interoceptive awareness (meta-d)	Interoceptive sensibility (BPQ_BA)	Interoceptive sensibility (BPQ_ANS)	Interoceptive sensibility (confidence)
0.256 (-0.445-2.166)	-0.313 (-1.351-0.653)	71 (30-125)	30.5 (21-47)	2.5 (1-4)

3.4.1.3 Part two: External performance

Exteroceptive accuracy (external task d-prime), calculated from hits (responding 'yes' to a trial including an omission) and false alarms (responding 'yes' to a trial without an omission), was significantly greater than zero on average across the group (Mdn=3.134, Range=1.334-4.520; Z = 630, *p* < .001, r_{rb} = 1.000, BF_{10} = 93.999), demonstrating that participants were attentive, as required by the task demands.

There was no significant difference between the external accuracy scores during perceived synchronous trials (M=3.011, SD=0.804) and perceived asynchronous trials (M=2.918, SD = 0.934; t(34) = 0.836, *p* = .409, Cohen's d' = 0.141, BF_{10} = 0.251), indicating that external performance was not influenced by heartbeat perception. There was no significant correlation between internal and external performance (r_s = 0.131, *p* = .455, BF_{10} = .291), further signifying that internal and external task performance is unrelated.

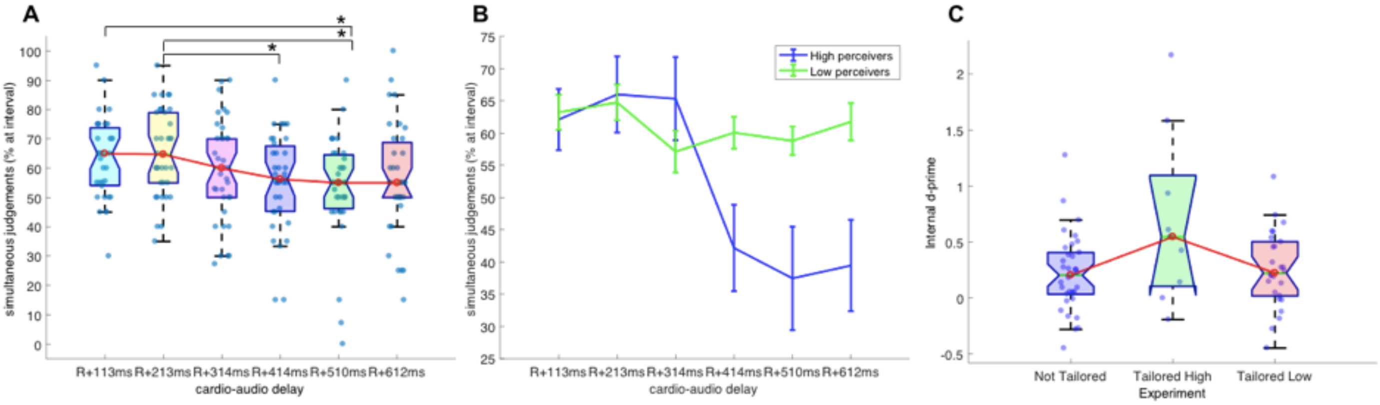


Figure 10. (A) boxplots of percentage preferences for each cardio-audio delay during the MCS, asterisks mark significant differences. (B) mean percentage preferences during the MCS split into high and low perceivers using Chi2, error bars reflect standard error of the mean. (C) boxplots of internal d' performance comparing experiment 1 ('Not Tailored' delays: Banellis & Cruse., 2020) with this experiment ('Tailored' delays) split into high and low heartbeat perceivers using Chi2 of MCS performance.

3.4.2 Event-related potentials

3.4.2.1 Part one: Method of constant stimuli

To test our hypothesis of reduced prediction error for sounds perceived as synchronous with the heart, we compared AEPs during cardio-audio delay trials most rated as synchronous with delay trials least rated as synchronous (comparison 1; see Supplementary Table 3 for analysis details). However, contrary to our hypothesis, we observed no significant AEP differences across perceived synchrony conditions (smallest *p* = .190).

Because there is an implicit omission for the first heartbeat after the end of each MCS trial, we also compared HEPs during periods of silence after the presentation of sounds to further test the hypothesis that HEPs reflect cardio-audio expectations. Specifically, we expected the first HEP during silent periods following a stream of stimuli perceived to be in cardio-audio synchrony to be larger relative to the HEP following stimuli perceived as asynchronous with the heartbeat. However, cluster-based permutation tests failed to reveal evidence of such expectation effects in this analysis when comparing the most rated synchronous trials with the least rated (R-locked: no clusters; omission-locked *p* = .248). Nevertheless, as the majority of participants (26) displayed a distribution of simultaneous choices at chance, it may not be meaningful to compare the most and least rated synchronous trials in this way. Subsequently, we exploratorily compared the MCS interval closest to the median of their simultaneous judgements with a 300ms later perceived asynchronous interval (as in the Part two HEP comparisons). While we didn't observe a pre-omission HEP effect of perceived synchrony in this analysis (small $p = .155$), we did observe an end-trial omission-locked perceived effect of synchrony (cluster extending 176-248ms, positive cluster $p = .004$), consistent with HEPs reflecting processes linked to cardio-audio integration.

As an exploratory analysis, we computed the above in high and low perceivers separately, as defined by the Chi^2 of each individual's MCS performance (comparison 3). When analysing AEPs in high heartbeat perceivers only (although only a small sample of 8 participants in part one, determined by a Chi^2 on individual MCS performance), we observe a larger early fronto-central positivity for trials perceived as synchronous (cluster extending 176-209ms, positive cluster $p = .021$), followed by a larger fronto-central negativity for perceived asynchronous trials (cluster extending 240-289ms, positive cluster $p = .007$) consistent with cardiac-driven auditory prediction error (see Figure 11). As all equivalent comparisons in low perceivers were not significant (smallest $p = .311$), this result is also consistent with a role of trait precision on HEP amplitude.

Source estimates of the initial AEP effect demonstrated the largest clusters in the left inferior frontal cortex and left temporopolar area, with smaller clusters including left premotor cortex and left primary sensory cortex. Source analysis of the following AEP effect demonstrated the largest clusters in the left inferior frontal cortex, bilateral anterior frontal cortex and left temporopolar area, with smaller clusters including left premotor cortex, right primary sensory cortex, bilateral visual association area.

All other ERP comparisons for part one (MCS) high perceivers were not significant (smallest $p = .046$, two-tailed test).

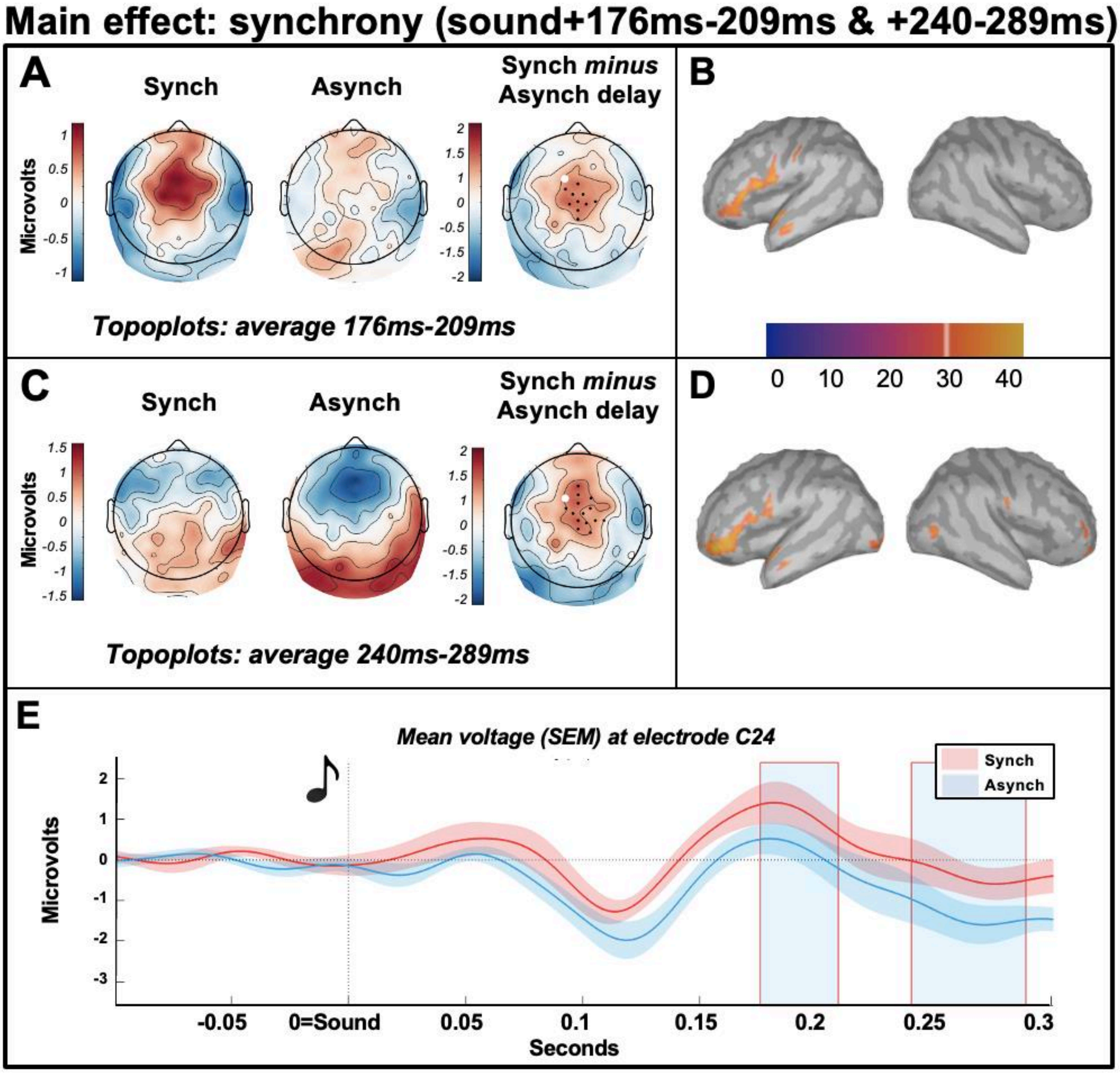


Figure 11. *Main effect of perceived synchrony from 176 to 209ms and 240 to 289ms relative to most (synch) and least (asynch) rated synchronous sounds during the MCS task (part 1), in high heartbeat perceivers only. Scalp distribution of the average significant difference across perceived synchrony conditions (A) 176-209ms and (C) 240-289ms with electrodes contributing to the cluster marked. (B) Estimated sources of the 176-209ms main effect include largest clusters in the left inferior frontal cortex and left temporopolar area, smaller clusters included left premotor cortex and left primary sensory cortex. (D) Estimated sources of the 240-289ms main effect include largest clusters in the left inferior frontal cortex, bilateral anterior frontal cortex and left temporopolar area, smaller clusters included left premotor cortex, right primary sensory cortex, bilateral visual association area. (E) average AEP across participants at electrode C24, light blue shaded regions represent the time of the significant positive effect. Note, no baseline correction was performed to avoid the insertion of differences which reflect the processing of the previous heartbeat or preparatory cardiac commands, however, with baseline correction the polarity of results may differ (see Supplementary Table 7 for analysis results with baseline correction).*

3.4.2.2 Part two: Individually-adjusted two-interval task

3.4.2.2.1 Cardio-audio expectation

To test our hypothesis of cardiac-driven expectations of sounds, we compared HEPs across cardio-audio delay conditions pre-omission. We observed a pre-omission main effect of delay (positive cluster *p* = .024) locked to the R-peak, replicating our previous finding with fixed cardio-audio delays and supporting our hypothesis of heartbeat-driven predictions of auditory stimuli (Banellis & Cruse, 2020). The positive cluster extended from 79-128ms. Source estimates of this effect include largest clusters in left middle temporal gyrus and right supramarginal gyrus and smaller clusters in bilateral frontal eye fields, left dorsolateral prefrontal cortex, left visual association area, right superior temporal gyrus and right fusiform gyrus (see Figure 12).

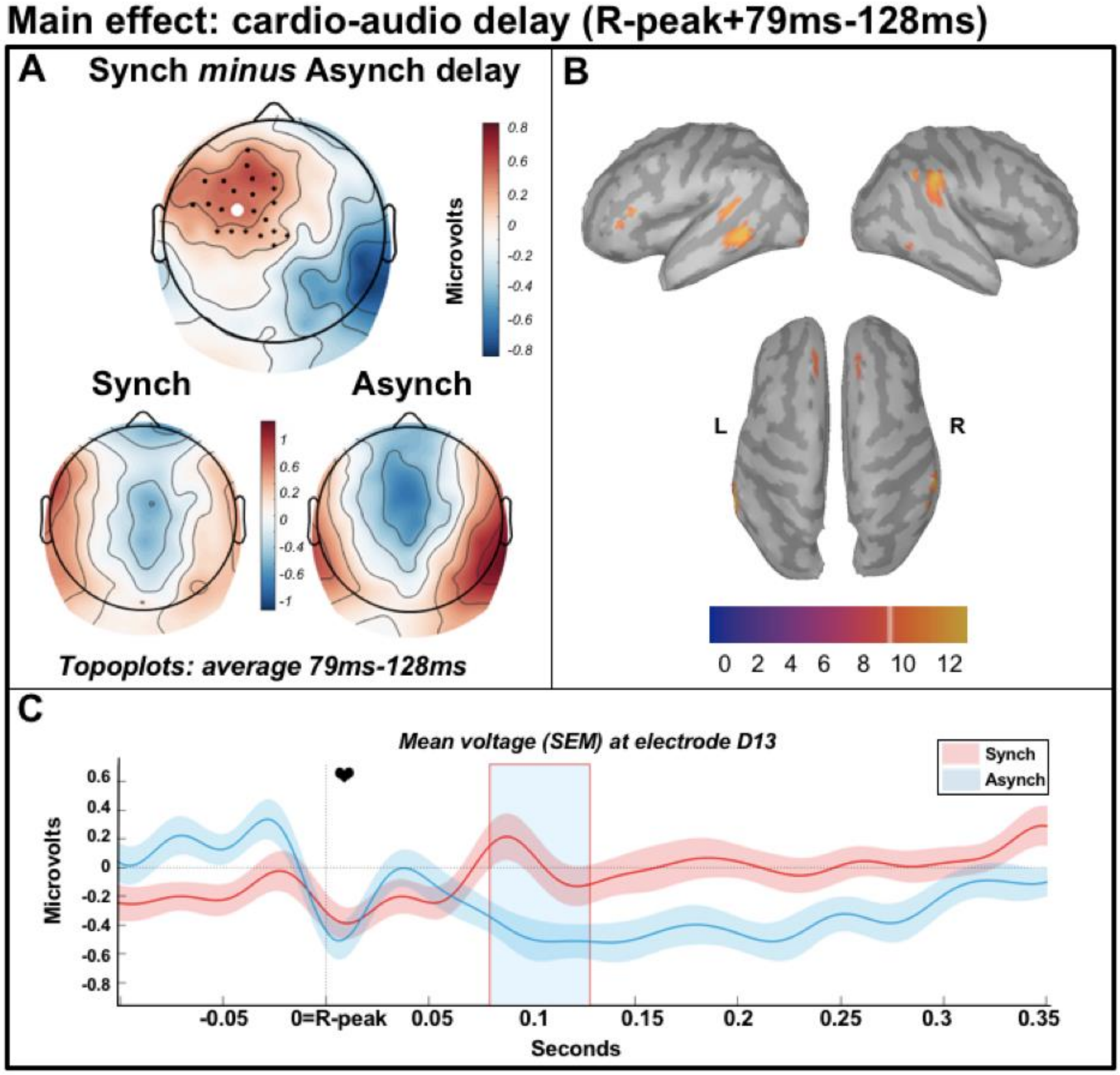


Figure 12. *Main effect of cardio-audio delay from 79 to 128ms relative to R-peak during pre-omission periods in the individually-adjusted two interval task (part 2). (A) Scalp distribution of the average significant difference across delay conditions 79-128ms, with electrodes contributing to the cluster marked. (B) Estimated sources of the main effect include largest clusters in left middle temporal gyrus and right supramarginal gyrus and smaller clusters in bilateral frontal eye fields, left dorsolateral prefrontal cortex, left visual association area, right superior temporal gyrus and right fusiform gyrus. (C) average HEP across participants at electrode D13, light blue shaded region represents the time of the significant positive effect. Note, no baseline correction was performed to avoid the insertion of differences which reflect the processing of the previous heartbeat or preparatory cardiac commands, however, with baseline correction the polarity of results may differ (see Supplementary Table 7 for analysis results with baseline correction).*

To test our hypothesis of attentional precision modulating predictive mechanisms, we calculated the attention and delay interaction as the difference between short-delay and long-delay trials between attention groups (i.e. a double-subtraction; comparison 4). However, we did not observe a significant R-locked delay and attention interaction (p = .401). Nevertheless, we observed a significant main effect of attention on pre-omission responses (negative cluster p = .013, cluster extending 37-68ms). Source estimates of this effect include largest clusters in left anterior prefrontal cortex and right visual association area, with smaller clusters in left dorsolateral prefrontal cortex and right fusiform gyrus (see Figure 13).

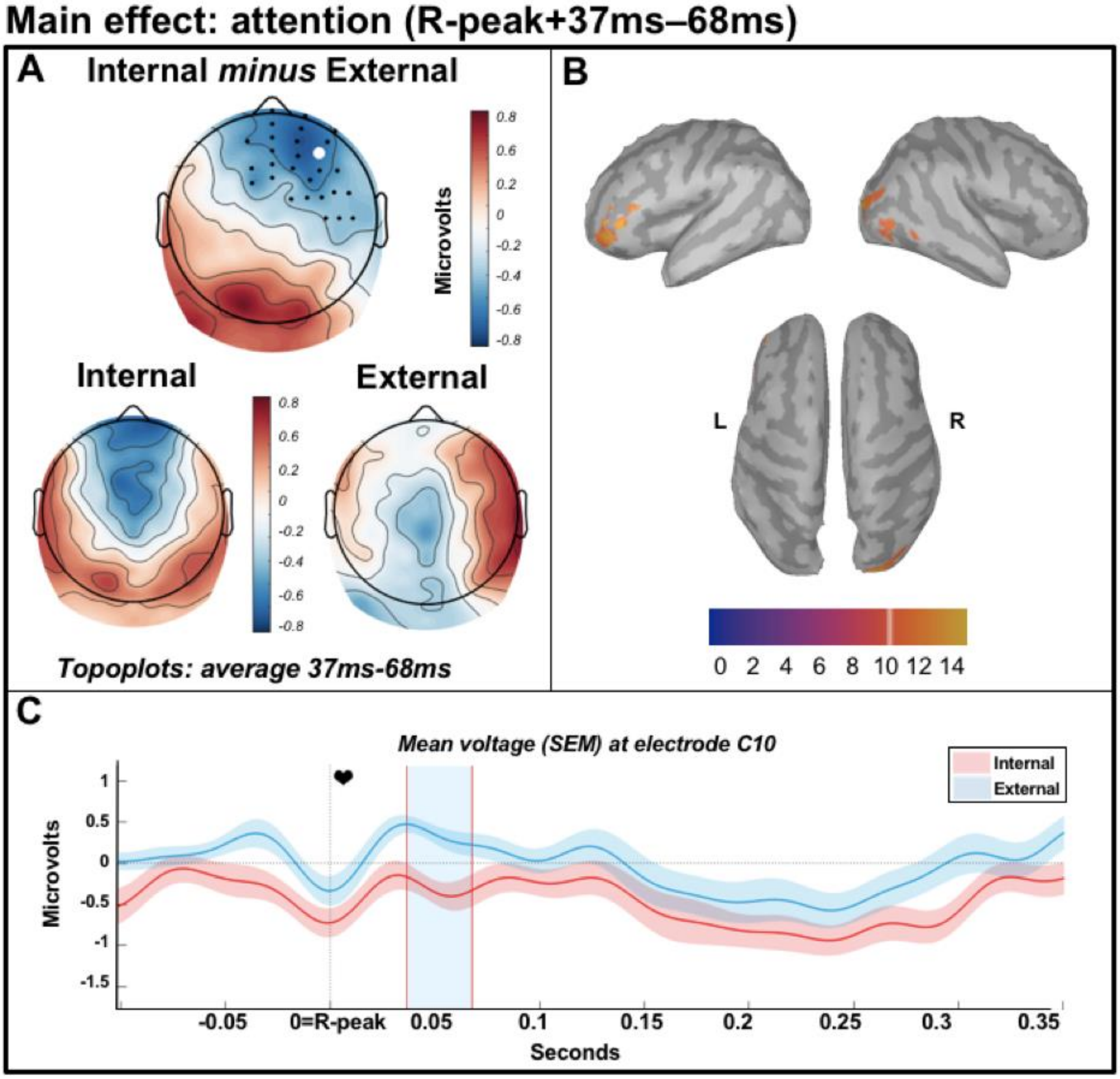


Figure 13. *Main effect of attention from 37 to 68ms relative to R-peak during pre-omission periods in the individually-adjusted two interval task (part 2). (A) Scalp distribution of the average significant difference across attention conditions 37-68ms, with electrodes contributing to the cluster marked. (B) Estimated sources of the main effect include largest clusters in left anterior prefrontal cortex and right visual association area, smaller clusters in left dorsolateral prefrontal cortex and right fusiform gyrus. (C) average HEP across participants at electrode C10, light blue shaded region represents the time of the significant negative effect. Note, no baseline correction was performed to avoid the insertion of differences which reflect the processing of the previous heartbeat or preparatory cardiac commands, however, with baseline correction the polarity of results may differ (see Supplementary Table 7 for analysis results with baseline correction).*

3.4.2.2.2 Unfulfilled expectation

Inconsistent with our hypothesis of attentional precision modulating predictive mechanisms, and inconsistent with evidence from a previous study (Banellis and Cruse, 2020), the attention and delay interaction for omission-locked responses was also not significant (p = .159). One potential cause of this lack of replication is that in this experiment we defined omissions to include not only within-task silent periods, but also silent periods at the end of trials without an omission to increase power. However, when we selected within-task omissions only and analysed the significant electrodes and time window of the delay and attention interaction from our previous study (Banellis & Cruse, 2020) this interaction is also not significant (F(1,32) = 2.141, p = .153, n^2 = 0.022, BF_{incl} = 0.100).

To test our hypothesis of higher prediction error during omission periods in a stream of auditory stimuli perceived as synchronous with the heart, we compared omission-evoked responses across cardio-audio delay conditions. We observed an omission-locked main effect of delay, with the positive cluster extending 94-137ms (positive cluster p = .022). Source estimates include largest clusters in left inferior frontal gyrus, right anterior frontal cortex, with smaller clusters in left superior temporal gyrus (see Figure 14).

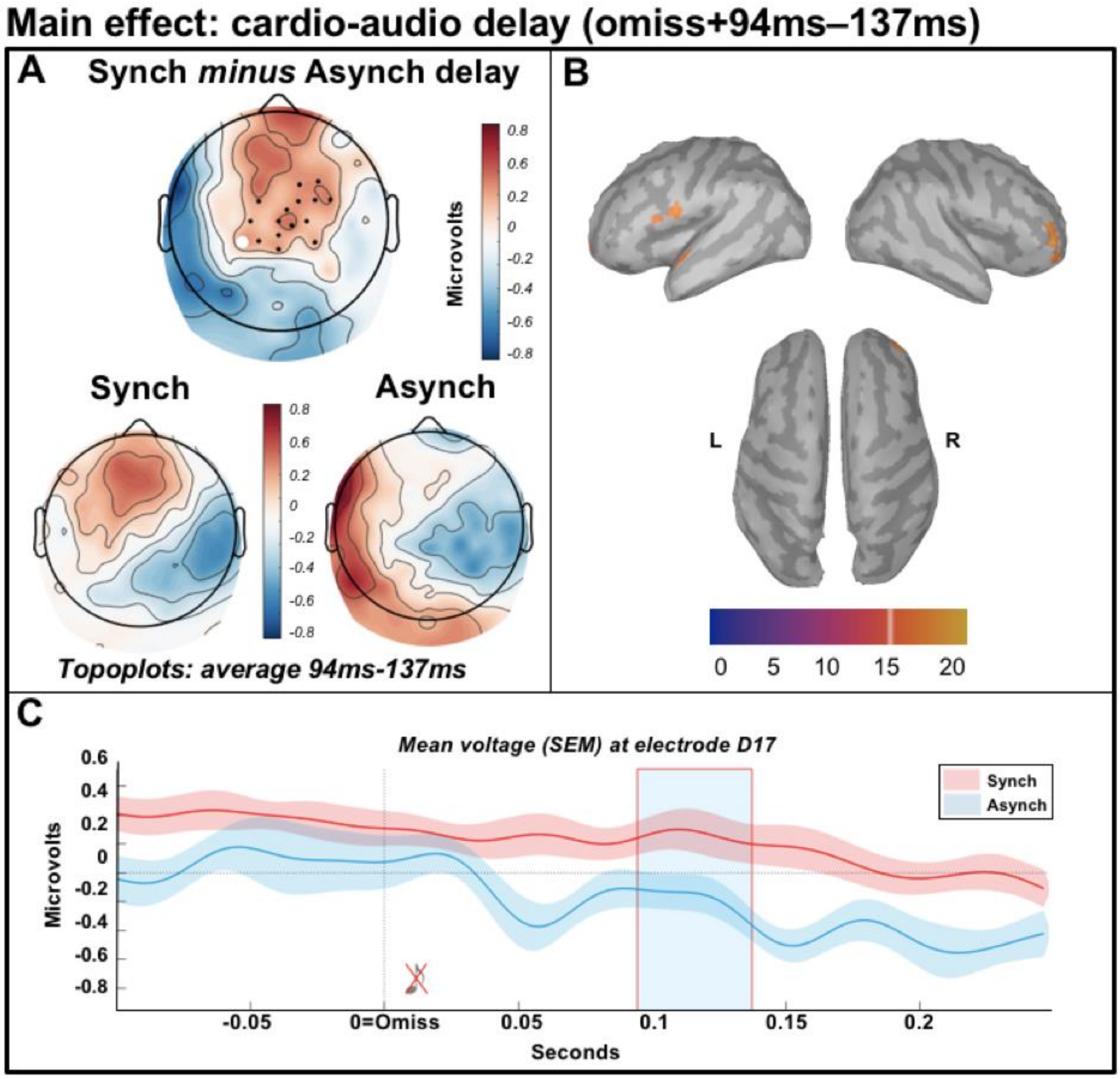


Figure 14. *Main effect of cardio-audio delay from 94 to 137ms relative to the omission during the individually-adjusted two interval task (part 2). (A) Scalp distribution of the average significant difference across delay conditions 94-137ms, with electrodes contributing to the cluster marked. (B) Estimated sources of the main effect include largest clusters in left inferior frontal gyrus, right anterior frontal cortex, smaller clusters in left superior temporal gyrus. (C) average omission-evoked response across participants at electrode D17, light blue shaded region represents the time of the significant positive effect. Note, no baseline correction was performed to avoid the insertion of differences which reflect the processing of the previous heartbeat or preparatory cardiac commands, however, with baseline correction the polarity of results may differ (see Supplementary Table 7 for analysis results with baseline correction).*

3.4.2.2.3 Interoceptive ability

For all evoked potential analyses, we separated our participants into groups of high/low interoceptive accuracy, sensibility, and awareness with median splits. First, we tested our hypothesis of interoceptive ability modulating the attention effect observed previously in Banellis

& Cruse (2020) (comparison 6). We observed a significant omission-locked interaction of interoceptive awareness and attention during synchronous trials (positive cluster *p* = .014, cluster extending 96-139ms). Source estimates of this effect include right frontal eye fields and bilateral visual association cortex. Pairwise comparisons of omission responses during synchronous trials revealed a significant difference between attention conditions in participants with high interoceptive awareness (negative cluster *p* = .019, cluster extending 105-131ms); no clusters were observed when comparing low awareness participants. Source estimates of the attention effect in high awareness participants reveal the left anterior frontal cortex, left dorsolateral prefrontal cortex and right visual association cortex. Source estimates of the same time-window in the low awareness group includes bilateral visual association cortex, right angular gyrus and right fusiform gyrus (see Figure 15).

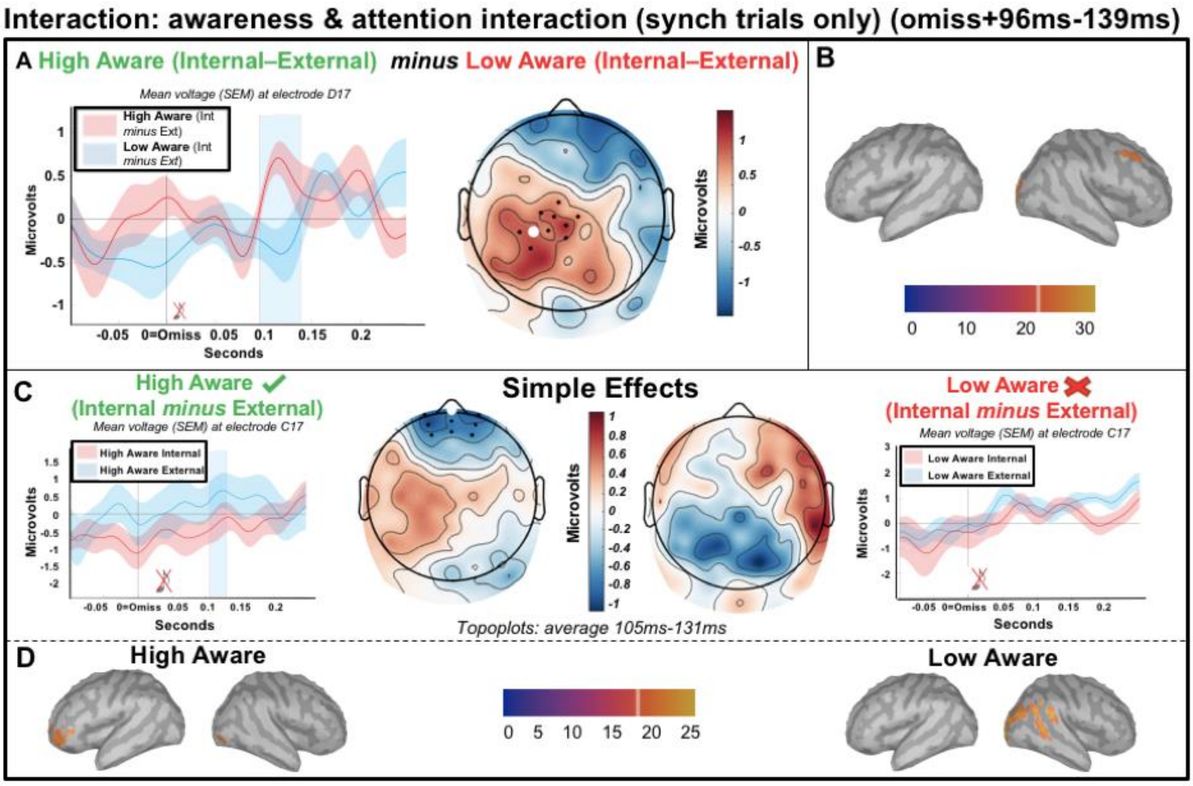


Figure 15. *Interaction of interoceptive awareness and attention from 96 to 139ms relative to the omission during synchronous trials only in the individually-adjusted two interval task (part 2). (A - left) Average omission-evoked response across participants at electrode D17, light blue shaded region represents the time of the significant effect. (A-right) Scalp distribution of the average significant interaction (awareness x attention) 96-139ms, with electrodes contributing to the cluster marked. (B) Estimated sources of the interaction include right frontal eye fields and bilateral visual association cortex. (C) Analysis of the simple effects showing qualitatively different topographic distributions across interoceptive awareness groups (105-131ms) and a significant effect of attention in high awareness participants only. (D-left) Estimated sources of high awareness simple effects analysis reveal the left anterior frontal cortex, left dorsolateral prefrontal cortex and right visual association cortex. (D-right) Estimated sources of low awareness simple effects analysis includes bilateral visual association cortex, right angular gyrus and right fusiform gyrus. Note, no baseline correction was performed to avoid the insertion of differences which reflect the processing of the previous heartbeat or preparatory cardiac commands, however, with baseline correction the polarity of results may differ (see Supplementary Table 7 for analysis results with baseline correction).*

All other omission-locked interoceptive ability interactions with attention during synchronous trials were not significant (interoceptive accuracy (smallest *p* = .097), interoceptive sensibility: median confidence (smallest *p* = .161), the awareness subsection (smallest *p* = .081) and the autonomic reactivity subsection (smallest *p* = .061) of the BPQ separately). Additionally, no significant R-locked interoceptive ability and attention interactions during synchronous trials were observed (smallest *p* = .099).

Next, we tested our hypothesis of interoceptive ability modulating the delay effect (comparison 5) and observed no omission-locked interactions during internal trials (interoceptive accuracy (no clusters), awareness (no clusters) or sensibility (median confidence (smallest *p* = .127), the awareness (smallest *p* = .350) and the autonomic reactivity (smallest *p* = .210) subsection of the BPQ separately). Additionally, no significant R-locked interoceptive ability and delay interactions during internal trials were observed (smallest *p* = .107).

Finally, we observed no significant correlations of interoceptive ability with the amplitude of the omission-locked delay effect (smallest *p* = .184). However, we observed an uncorrected significant correlation of the awareness subsection of the BPQ and the R-locked delay effect during external attention (*p* = .022), however this is 1 out of the 16 correlations (bonferroni corrected alpha = .003). All other correlations of interoceptive ability and the R-locked delay effect were not significant (smallest *p* = .233).

3.5 Discussion

Interoceptive and exteroceptive integration is fundamental for the interwoven interactive experience of the body with the external world. These integrated signals are proposed to operate predictively, with regulation by precision-weighting (Barrett & Simmons, 2015; Cameron, 2002; Seth, 2013; Seth et al., 2012; Seth & Friston, 2016). In a previous study, we observed integrated cardio-audio predictive mechanisms by studying HEPs during heartbeat-predicted omissions (Banellis & Cruse, 2020), While our data in that study were consistent with the modulation of HEPs by attentional precision, we found no evidence of the influence of trait precision – i.e., individual interoceptive ability – contrary to the expectations of predictive coding. Consequently, in this study, we tailored the cardio-audio delays used for each individual to more accurately investigate trait precision modulations of predictive signals, and subsequently determine if intero-extero integration operates in accordance with the predictive coding framework.

Despite our use of an arguably more sensitive and individually-tailored heartbeat perception task, we found no evidence for an HEP relationship between any measure of interoceptive ability and cardio-audio delay. One interpretation is that this may be due to the difficulties of assessing interoceptive performance, as we assess this indirectly with a relatively difficult task. For example, even with a more sensitive measure of objective performance across multiple cardio-audio delay intervals, only 9/35 participants were classified as high heartbeat perceivers. Additionally, influences of interoceptive ability may occur much later than can be observed with our design. For example, ERPs associated with metacognition often occur up to

1900ms post-stimulus, thus overlapping with forthcoming heartbeats and/or sounds (Skavhaug et al., 2010; Sommer et al., 1995; Tsalas et al., 2018). Furthermore, metacognitive awareness may be reflected in other features of the EEG, such as global long-range connectivity patterns, rather than local HEP differences (Canales-Johnson et al., 2015). Our specific HEP results here, nevertheless, fail to support a predictive coding account of interoceptive-exteroceptive integration under which predictive processes are modulated by trait level precision.

Furthermore, we also failed to replicate the previously reported attention and delay interaction of omission-evoked potentials, contrary to a predictive coding account in which attention modulates expectations by precision-weighting. One possible interpretation is that, in this study, participants relied less on attentional-precision to 'boost' their predictions due to the enhanced perception of cardio-audio synchrony, reflected in the trend for increased performance relative to the previous experiment (see Figure 10). As a result, attentional modulations of HEPs may have been weaker in this study. Despite this, we did observe a significant omission-locked delay effect, demonstrating the presence of cardio-audio predictive mechanisms, although without evidence of attentional modulation (see Figure 14). This is comparable to findings by Pfieffer and De Lucia (2017) who also found an HEP difference during omission periods when comparing cardio-audio synchronous streams with asynchronous streams in participants who were not actively attending to cardio-audio synchronicity. However, in that study, due to the timing of the auditory stimuli, it was not possible to separate omission-evoked effects from expectation effects. While we overcame this in our study by employing cardio-audio delays, allowing for the independent investigation of expectation and unfulfilled expectation effects, we also observe no evidence of the necessity of attention for generating auditory expectations on the basis of the heartbeat. Indeed, despite our previous observations (Banellis & Cruse, 2020), our Bayesian analysis in this study indicated strong evidence (i.e. BF=10 in favour of the null) for the absence of an interaction with attention – inconsistent with a predictive coding account.

Upon visual inspection of our data, we were concerned about the presence of HEP differences prior to omissions in some comparisons, in particular that shown in Figure 14. These baseline differences may subsequently confound any apparent post-omission effects. Due to the cyclical nature of the heartbeat, and to be consistent with some previous literature (Azzalini et al., 2019; Babo-Rebelo et al., 2016, 2019; Banellis & Cruse, 2020; Park et al., 2014a; Petzschner et al., 2019), we did not apply baseline correction in our pre-processing above. However, this choice is not ubiquitous in the HEP literature. Indeed, the issues for replication that are posed by the range of pre-processing / analysis / CFA correction methods employed across the field have recently been highlighted (Coll et al., 2021; Park & Blanke, 2019). Consequently, we re-analysed all effects reported here using an additional five sets of pre-processing pipelines (e.g., with baseline correction / without CFA correction, etc.; see Supplementary Table 7 for details) to identify the consistency of our observed effects (Botvinik-Nezer et al., 2020; Simonsohn et al., 2015; Steegen et al., 2016). We were reassured to find that the post-omission delay effect remains significant across all pre-processing pipelines, strengthening our interpretation that it reflects cross-modal integrative predictive processes, rather than analytical confounds (see Supplementary Figure 19).

Additionally, we replicated our previously observed pre-omission HEP difference across cardio-audio delay trials, likely reflecting a difference in cardio-audio expectation and supporting the hypothesis of interoceptive signals guiding expectations of exteroceptive stimuli (see Figure 12). However, the scalp topography and estimated sources of the pre-omission delay effect here are not entirely overlapping with those observed previously. For example, although source estimates from both studies revealed the middle temporal gyrus, supramarginal gyrus, and broad frontal regions, somatosensory and motor regions were also evident in Banellis and Cruse (2020), while visual and fusiform areas were evident in this study only. One possible reason for this disparity is that the previously reported expectation effect (Banellis & Cruse, 2020) extended to 230ms post-R, while the pre-omission window in this study was necessarily shorter (R+129ms) due to our use of individualised delays. Nevertheless, the topographical differences across experiments persist even when using a shorter time-window in our previous study. It may therefore be that our use of tailored delays in this study enhanced heartbeat-driven expectations in more participants, as supported by the trend for better objective performance, thus more accurately reflecting cross-modal expectations and subsequent predictive sources.

Although not interacting with cardio-audio delay, we did observe some evidence of the influence of interoceptive ability on HEPs in our omission-locked interaction of attention with interoceptive awareness (see Figure 15). This significant interaction reflected an attentional difference in high awareness participants only. Consistent with this result, previous research has reported a greater attentional HEP difference in good heartbeat perceivers, relative to poor perceivers (Montoya et al., 1993; Yuan et al., 2007). However, rather than the heartbeat discrimination task we employed here, those previous studies used the heartbeat counting task, which problematically confounds heartbeat perception with the ability to estimate heartrate or time (Brener & Ring, 2016; Ring & Brener, 2018). The effect observed here temporally overlaps with an effect of delay, potentially indicating that with high awareness, attention alters intero-extero predictive mechanisms. However, this effect was present in only a subset of the pre-processing pipelines, thus requiring cautious interpretation. Indeed, when studying neural activity time-locked to bodily events, it is crucial to test for the confounding influence of both peripheral physiological signals and analytical decisions. For example, we observed no heartrate or HRV differences in the directions of interest, and no ECG differences across conditions of interest for all analyses reported here, giving us confidence that our results reflect neural activity. Conversely, the behaviour of HEP effects across multiple pre-processing pipelines provides a valuable indicator of confidence in the observed effects. As described above, standardisation and understanding of HEP pre-processing and analyses are vital for the progress of the field (Bigdely-Shamlo et al., 2016; Coll et al., 2021a; Farzan et al., 2017).

Despite our lack of evidence for precision-weighting of HEPs by either attention or interoceptive ability, the robust pre- and post-omission delay effects observed here (and previously; Banellis and Cruse, 2020), are consistent with HEPs reflecting aspects of an integrated cardio-audio expectation process. Some accounts describe intero-extero expectation mechanisms as fundamental for embodied selfhood, emotion, and the generation of an integrated first-person perspective (Azzalini et al., 2019; Seth, 2013; Seth et al., 2012; Seth & Friston, 2016). Therefore, our paradigm may provide a tool for investigating cross-modal expectation processes in clinical conditions, as well as assessing its influence on cognition.

In conclusion, here we replicate evidence of cardiac signals guiding expectations of auditory stimuli. Despite this, we observe no evidence of either attentional-precision or trait precision modulating these predictive processes, suggesting that intero-extero integration may not operate entirely within a precision-weighted predictive coding framework. Our results demonstrate a need for a clearer definition of the manipulation and measurement of precision on HEP effects, and the specific predictions made by predictive coding theories more generally. Finally, the robust delay effects observed here, and previously, may be useful for the investigation of the role of intero-extero integration in cognition, as well as for assessing its dysfunction in clinical groups.

CHAPTER 4: THE PROGNOSTIC UTILITY OF HEART-EVOKED POTENTIALS IN ACUTE UNRESPONSIVE PATIENTS

3.1 Abstract

Predicting recovery of consciousness after severe brain injury is a challenge of modern medicine, with implications for care and rehabilitation decisions. Such disorders of consciousness are defined as having dysfunctional awareness of the environment and the self. Despite the dual diagnostic criteria of consciousness, research has focused almost exclusively on responses to exteroceptive stimuli. Yet, the processing of visceral signals from the body (i.e., interoception) is vital for embodied selfhood, emotional experience, and a unified first-person perspective. Indeed, heart-evoked potentials (HEPs) covary with perceptual consciousness, self-recognition, bodily self-consciousness, and self-processing dimensions. Thus, we hypothesised their detection would predict the recovery of conscious self-related processes. Here, we investigated the prognostic potential of resting HEPs and cardiac measures in acute unresponsive patients in the intensive care unit. We did not find convincing evidence of HEP amplitude, HEP variance across time, or cardiac measures predicting outcome from unresponsiveness, three and six months post-assessment. However, we had a reasonably small sample with low variability in consciousness outcome. Thus, a larger sample with greater variability in outcome may reveal alternative results. We suggest potential avenues for future prognostic research, including investigating HEPs and cardiac measures during self-cognitive paradigms, as well as perturbatory vagus nerve stimulation techniques.

Key words:

Heart-evoked potentials, cardiac activity, interoception, prognosis, disorders of consciousness, acute unresponsiveness.

3.2 Introduction

~Twenty patients are admitted to UK intensive care units from a traumatic brain injury each day (NICE., 2014; Schnakers et al., 2009). These patients often enter a state of compromised consciousness, characterised by a lack of awareness of the self and the environment. Despite dual classifications of awareness (i.e., of environment and self), prognostic research has focused almost exclusively on external perceptual awareness, leaving internal self-awareness largely unexplored (Azabou, Navarro, et al., 2018; Jain & Ramakrishnan, 2020; Pascarella et al., 2018). The assessment of all aspects of awareness, including external and internal awareness, is paramount for improving prognostic and diagnostic accuracy in unresponsive patients. Accurate prognostication is particularly important as it reduces uncertainty for critical care decisions such as rehabilitation or life-sustaining therapy assignment, wherein the window of opportunity is narrow (Kitzinger & Kitzinger, 2018).

A wealth of evidence indicates the importance of internal bodily signals (i.e., interoception) for embodied selfhood, emotional experience, and a unified first-person perspective (Azzalini et al., 2019; Craig, 2009; Critchley & Garfinkel, 2018; A. Damasio, 2010; Seth & Friston, 2016). This supports embodied cognition frameworks that describe the body as a fundamental component of self-cognition and consciousness, suggesting self-related bodily signals may provide prognostic promise of self-awareness in unresponsive patients (Barrett & Simmons, 2015; Seth, 2013; Seth et al., 2012). Brain-heart interactions are the most extensively researched visceral component of self-awareness. Indeed, the integration of cardiac signals with visual bodily-related stimuli enhances numerous aspects of self-processing. For example, pulsing a virtual body image synchronously with the heartbeat enhances the sense of ownership and shifts the perceived location of self towards the simulated body (Aspell et al., 2013; Heydrich et al., 2018; Suzuki et al., 2013). Additionally, synchronous cardiac stimulation increases self-identification with facial features of an other's image (Sel et al., 2017). Furthermore, an individual's ability to sense their heartbeat modulates self-consciousness during these bodily illusions, further demonstrating the importance of cardiac signals for self-processing (Sel et al., 2017; Suzuki et al., 2013; Tajadura-Jiménez et al., 2012; Tsakiris & Critchley, 2016).

One method of measuring neural processing of cardiac signals is via heart-evoked potentials (HEPs) - neural electrophysiological responses locked to the heartbeat. HEPs have been associated with broad conscious phenomena. For example, HEPs predict the detection of visual and somatosensory stimuli into perceptual conscious awareness (Al et al., 2020; Park et al., 2014). HEPs correlate with illusory bodily self-consciousness during full-body illusions and vary with synchronous and asynchronous visuotactile stimulation during these illusions (Park et al., 2016, 2018). Furthermore, HEPs fluctuate with imagined perspective when comparing periods of imagining ourselves from a first-person perspective with imagining a familiar other from a third-person others perspective (Babo-Rebelo et al., 2019). Finally, HEPs covary with ratings of the self-relatedness of spontaneous thoughts, as well as with ratings of the first-person perspective nature of these thoughts (Babo-Rebelo et al., 2016). Thus, HEPs provide a means of investigating conscious self-cognition in unresponsive patients. Furthermore, findings from Chapters 2-3 demonstrate HEPs reveal mechanisms of interoceptive-exteroceptive integration, fundamental for pre-reflexive aspects of selfhood (Banellis & Cruse, 2020, 2021). Mechanistically, HEPs have multifaceted potential contributing sources, including baroreceptors in arteries, cardiac afferent neurons in the heart wall, somatosensory mapping through the skin, and neurovascular coupling in the brain (Park & Blanke, 2019). These broad contributing mechanisms may explain the diverse spatial and temporal extent of HEP components. However, the lack of standardised preprocessing/analysis procedures also contributes to the variability of HEP characteristics (Coll et al., 2021a).

Importantly, recent evidence highlighted the diagnostic value of HEPs in prolonged disorders of consciousness. For example, Raimondo et al (2017) observed two topographically distinct HEP differences between minimally conscious state (MCS) and vegetative state/unresponsive wakefulness syndrome (VS/UWS) patients. The early HEP difference (i.e., 144-340ms post-R-peak) was characteristic of the cardiac field artefact (CFA) of the T-wave (i.e., left-posterior positivity and right-frontal negativity), followed by a later central positivity difference (i.e., 340-540ms post-R-peak). As described, this study did not remove the CFA from HEP responses; thus, differences may reflect low-level electrical influences from the heart instead of the brain. Nevertheless, this study highlights the value of cardiac information for consciousness classification. Candia-Rivera et al (2021) used machine learning to classify CFA-corrected HEP responses of VS/UWS and MCS patients. They found that resting-state HEP amplitude and variance distinguished between VS/UWS and MCS patients with high accuracy (accuracy 87%, sensitivity 96%; specificity 50%) (Candia-Rivera et al., 2021). Notably, consciousness classification using HEPs was higher than when using random EEG segments not locked to the cardiac cycle, suggesting brain responses to heartbeats convey additional information regarding consciousness than residual brain activity. However, the number of VS/UWS and MCS was largely unbalanced in that study (7 VS/UWS vs 31 MCS), which may bias classification accuracy when using a machine learning approach. Although authors perform a permutation test to confirm that validated accuracies are greater than chance, a mass-univariate approach may have been more appropriate.

Furthermore, the HEP classifications in Candia-Rivera et al (2021) provided a graded HEP-consciousness score, computed from the proportion of trees that predicted MCS diagnosis (i.e., based on a random forest classifier). Low HEP-consciousness scores were present more frequently in patients diagnosed as MCS neurologically (i.e., brain glucose metabolism via PET) but not behaviourally (i.e., CRS-R). Moreover, HEP classification was higher when consciousness diagnoses were based on brain metabolism than behaviour (although both performed with high accuracy), suggesting HEPs indicate an aspect of consciousness not necessarily reflected in behavioural responses. Although diagnoses based on brain glucose metabolism are advantageous for patients who cannot behaviourally respond, high brain metabolism may reflect healthier neuronal functioning rather than consciousness state. Nevertheless, correlations of brain glucose metabolism and consciousness-HEP scores were not localised to arousal/salience brain regions which would be expected if HEP/PET classification reflected overall brain state. Instead, HEP-consciousness scores correlated with brain glucose metabolism in the right superior temporal sulcus of the default mode network, which is loosely associated with social and self-cognition, and the right occipitotemporal cortex related to face and object recognition.

HEPs provide information regarding how the brain responds to ascending cardiac signals. In contrast, lower-level measures of cardiac activity (i.e., heart rate variability and heart rate) reflect descending neural modulation of peripheral autonomic systems. Thus, these cardiac measures demonstrate preserved autonomic system functioning and subsequently can be useful for diagnosis after severe brain injury (Baguley et al., 2006). Specifically, heart rate or heart rate variability have distinguished between VS/UWS and MCS during nociceptive stimulation (Leo et al., 2016; Riganello et al., 2019; Tobaldini et al., 2018), emotionally valenced stimuli (i.e., familiar voice/presence and music) (Riganello et al., 2010, 2011, 2015), during sleep/sedation (Larroque et al., 2019; Leo et al., 2016; Riganello et al., 2018) and rest (Riganello et al., 2021). However, some studies have observed no heart-rate or heart-rate variability differences in VS/UWS and MCS patients during rest (Candia-Rivera et al., 2021; Raimondo et al., 2017). Furthermore, Raimondo et al (2017) observed cardiac phase shifts during global auditory pattern violations in MCS patients, but not VS patients. Notably, these cardiac-phase shifts during auditory stimulation significantly improved consciousness classification when combined with EEG-consciousness markers than EEG-markers alone (Raimondo et al., 2017). Thus, descending brain-heart measures can provide valuable information for consciousness diagnoses.

Although critical evidence supports the diagnostic potential of HEPs and cardiac measures in chronic disorders of consciousness patients, little research has been conducted on their prognostic utility from acute unresponsive states. This is particularly important because acute unresponsive patients have demonstrated EEG evidence of command following, despite being behaviourally diagnosed as unresponsive (Claassen et al., 2019; Edlow et al., 2017). In fact, this was the case for 15% of acute behaviourally unresponsive patients, which is similar to the percentage of cognitive motor dissociation diagnoses in chronic disorder of consciousness patients (Claassen et al., 2019; Kondziella et al., 2016). Furthermore, early detection of covert consciousness in the intensive care unit predicted functional outcome at one year (Edlow et al., 2021). Thus, acute unresponsive patients who demonstrate early neural evidence of consciousness may translate to a better functional recovery later.

To date, prognostic research in acute unresponsive patients has exclusively focused on responses to external perceptual stimuli (i.e., visual, auditory, somatosensory responses), leaving self-awareness largely unexplored (Carter & Butt, 2005; Zhu et al., 2019). These responses reflect the integrity of external sensory pathways, revealing the extent of brain injury on external perceptual networks. Research is needed on the preservation of internal self-related networks, demonstrating the potential for recovery of conscious self-cognitive mechanisms. Thus, we determine the prognostic potential of HEPs and cardiac measures for the recovery of consciousness from acute unresponsive states. This is important as measuring interoceptive processing may provide a method of assessing internal self-related aspects of awareness, an under-researched but critical component of the consciousness diagnostic criteria. Measuring brain-heart interactions may predict a positive recovery in two ways: either by detecting conscious internal self-cognitive mechanisms in patients who are covertly self-aware but unresponsive (and therefore more likely to recover behaviourally) or by detecting unconscious preserved internal self-cognition networks which may support the recovery of self-awareness later. Thus, we hypothesise HEP amplitude and variance will predict consciousness outcome from acute unresponsive states at three and six months post-assessment, potentially via embodied self-cognitive mechanisms. Determining a neural method of assessing the recovery of self-awareness will accompany those of external perceptual awareness, which will subsequently improve clinical procedures that significantly enhance the quality of life of unresponsive patients and caregivers (Edlow et al., 2021; Young et al., 2021). Furthermore, we predict cardiac measures such as heart rate and heart rate variability to also predict recovery from unresponsiveness by determining the preservation of descending brain-heart pathways.

3.3 Methodology

3.3.1 Participants

We screened 139 traumatic brain-injured patients from the intensive care unit at Queen Elizabeth Hospital Birmingham between April 2018 and October 2019. The inclusion criteria required patients to have a traumatic brain injury (TBI), to be over 18 years old, and to have a Glasgow Coma Scale (GCS) motor score below 6 (i.e., no behavioural command following). We excluded patients if they had a history of moderate to severe TBI or neurological disorder, were moribund, had hearing impairments, were not an English speaker, had a CT brainstem-only lesion (i.e., potential locked-in syndrome patient), or CT evidence of a focal left lateral temporal lobe lesion (i.e., potential language deficit) (language/hearing requirements due to auditory stimulation in other parts of the protocol).

We received consent for 28 patients to participate in the study, and 21 were eligible at the time of EEG (48 hours to 7 days after sedation hold). After excluding the data of 2 patients due to artefacts/technical issues, the outcome assessments of 17 patients were available at 3 months post-EEG (median = 3 months + 5 days, range = 2 months + 29 days to 4 months + 1 day) and 16 patients were available at 6 months post-EEG (median = 6 months + 4 days, range = 5 months + 29 days to 7 months + 18 days). 5 patients had sinus tachycardia (i.e., faster than average sinus rhythm), and all others had no cardiac abnormalities. All patients were not obeying commands (GCS motor subscale below 6) between the time of sedation and the EEG, reflecting a sustained lack of behaviour rather than a transient fluctuation. See Table 3 for patient characteristic details (summary at 3 months: median age: 59, range 20–82; 2 females; summary at 6 months: median age: 56.5, range 20–82; 2 females).

This study was approved by the West Midlands Coventry and Warwickshire Research Ethics Committee, the Health Research Authority, and was sponsored by the University of Birmingham, England. The clinical team identified and approached personal or nominated consultees of each patient for written consent (for the initial patient EEG and later outcome interviews with consultees). The subset of patients who regained consciousness during the follow-up period were re-consented. The study was coordinated by the Surgical Reconstruction and Microbiology Research Centre, University Hospitals Birmingham.

Table 3. *Patient characteristics.*

Patient	**Sex**	**Age (yr)**	**GCS EEG (E/V/M)**	**Days after injury**	**CT grade**	**Average HEP amplitude (211ms)**	**3-month outcome**	**6-month outcome**
1	M	**72**	1/1T/3	**5**	**2**	-0.393	Death (1)	Death (1)
2	M	**26**	1/1/4	**17**	**5**	0.094	Vegetative state (2)	Vegetative state (2)

3	M	**40**	1/1T/3	**12**	**5**	-0.523	Lower severe disability (3)	Lower severe disability (3)
4	M	**59**	3/1/1	**13**	**5**	-0.156	Lower severe disability (3)	Lower severe disability (3)
5	F	**44**	1/1T/4	**10**	**5**	0.014	Lower severe disability (3)	Lower severe disability (3)
6	M	**82**	1/1T/1	**3**	**5**	0.289	Vegetative state (2)	Lower severe disability (3)
7	M	**20**	4/2/5	**17**	**6**	-0.024	Upper severe disability (4)	Upper severe disability (4)
8	M	**70**	1/1/4	**5**	**5**	-1.674	Lower severe disability (3)	Vegetative state (2)
9	M	**24**	2/1/5	**24**	**5**	-0.630	Lower severe disability (3)	Upper severe disability (4)
10	M	**70**	4/1/5	**10**	**6**	0.036	Upper moderate disability (6)	Lower good recovery (7)
11	M	**27**	2/1/4	**19**	**2**	-1.187	Lower severe disability (3)	Lower severe disability (3)
12	M	**77**	1/1T/4	**12**	**2**	-0.513	Lower severe disability (3)	Lower severe disability (3)
13	M	**54**	1/1T/4	**10**	**2**	0.555	Upper moderate	Upper moderate

							disability (6)	disability (6)
14	M	**59**	1/1T/4	**9**	**3**	-1.015	Lower severe disability (3)	-
15	F	**59**	4/1T/3	**14**	**5**	0.489	Lower severe disability (3)	Lower severe disability (3)
16	M	**61**	4/1T/3	**15**	**2**	-0.107	Upper severe disability (4)	Upper moderate disability (6)
17	M	**32**	4/1T/5	**17**	**2**	0.063	Upper severe disability (4)	Lower moderate disability (5)

3.3.2 EEG/ECG acquisition

A clinical electrophysiologist recorded EEG data at 256Hz or 512Hz, using a 19-electrode clinically certified EEG system, with an XlTek Brain Monitor EEG amplifier (Natus Medical Incorporated, Pleasanton, USA). The set-up included a 10/20 EEG montage, with additional right and left mastoid electrodes and a further two ECG electrodes placed on either side of the chest. The ground and reference electrodes were placed across the vertex. Data quality was monitored during acquisition and in subsequent offline artefact correction. We recorded between 5 and 10 min of resting-state data per patient, dependent on the level of agitation or immediate care needs (HEPs: median R-peaks = 286, range = 108-609; ECG: median R-peaks = 553, range = 318-864).

3.3.3 ECG preprocessing

We filtered the ECG data between 0.5 and 150Hz (however, a 120Hz low pass was used for three patients due to a lower sampling rate (256Hz) during acquisition), using the finite impulse response filter implemented in EEGLAB (function: pop_eegfiltnew). Also, we filtered the line noise from the ECG at 48-52Hz.

3.3.4 Heartbeat detection

We detected R-peaks from the ECG recordings using custom-written Matlab scripts (all openly available: https://osf.io/t2uxw/). First, we filtered the ECG signal between 1 and 40Hz. We accounted for ECG individual differences by transforming the ECG differently depending on the relative size of ECG components. For example, if R-peaks were larger than S-peaks, we computed the square of the z-scored ECG, whereas if S-peaks were larger than R-peaks, we calculated the z-score without squaring. Then, we created an ECG template by performing an initial R-peak detection using a z-score threshold of 10 (however, if T-waves were larger than R-peaks, a low and high R-peak threshold was defined to create the ECG template). If necessary, we adjusted the R-peak threshold to create a more accurate ECG template after visual inspection. We convolved the ECG template with the whole ECG time series and normalised the convolved ECG to have a maximum of 1. We identified R-peaks using a threshold of 0.6 proportion of maximum correlation from the convolved ECG, but adjusted the threshold if necessary, and enforced a minimum distance of 350ms between peaks. If outliers persisted, we visually inspected identified R-peaks and manually adjusted them if necessary.

Once R-peaks were identified, we segmented the EEG into epochs -300ms to 900ms relative to the R-peak of the ECG recording. We checked the epoched ECG for any remaining R-peak detection errors and manually corrected any final errors.

3.3.5 EEG preprocessing

We filtered the EEG data in two steps (i.e., high-pass then low-pass) between 0.5 and 40Hz and filtered the line noise from the EEG (48-52Hz). We manually removed trials or channels with excessively high voltages via visual inspection. We performed independent component analysis (ICA) to remove stationary oculomotor artefacts such as blinks and eye movements (using the *runica* function of EEGLAB).

We subjected the data to a second round of ICA to remove the cardiac field artefact (CFA). First, for the ICA computation, we filtered the ECG between 0.5Hz and 40Hz to ensure equivalent filtering as the EEG data and segmented the data into smaller epochs (-200ms to 200ms) with respect to the R-peak. We completed ICA on the shorter epoched data using the *runica* function of fieldtrip. To prevent multiple components with identical or symmetrical topographies, we set the maximum number of components to the rank of the data after trials concatenated. To select CFA components, we computed the pairwise phase coherence (PPC) of each component with the ECG. We selected a component if its PPC exceeded three standard deviations above the mean PPC of all components within the 0-25Hz range (however, for two patients, we lowered the identification threshold to two standard deviations above mean PPC, as no initial components were identified). We completed this selection procedure iteratively until no more than three components were selected. After visual inspection to ensure non-neural components had been identified, we removed the selected components from the original -300ms-900ms preprocessed EEG data. Finally, we visually inspected the data before and after CFA correction, and if the CFA was not visually diminished, we completed the cardiac ICA procedure again. The median number of components rejected across participants was 1 (range = 1-2).

Next, we interpolated the rejected channels using the triangulation method in fieldtrip and downsampled the data to 256Hz to ensure an equivalent sampling rate for all patients. We computed a robust average of each patient's HEPs using the default parameters of SPM12. Robust averaging down-weights outlier values iteratively by time-point to improve the estimation of the mean across trials. As recommended by SPM12, the resulting HEP was low-pass filtered below 20 Hz (again, with EEGLAB’s pop_neweegfilt). Finally, we average referenced the data and averaged each patient's HEP across frontocentral channels (C3, CZ, C4, F3, FZ, & F4), consistent with previously reported centrofrontal HEP effects (Canales-Johnson et al., 2015; MacKinnon et al., 2013; Schandry et al., 1986; Villena-González et al., 2017). We did not apply any baseline correction as cardiac activity is cyclical by nature and, therefore, may insert artifactual effects in the post-R-peak data (Park et al. 2014; Babo-Rebelo et al. 2016, 2019; Azzalini et al. 2019).

3.3.6 Glasgow Outcome Scale Extended Outcome Data

We conducted trimonthly outcome assessment with patients or consultees for a year via the telephone, using the Glasgow Outcome Scale Extended (GOSE; Teasdale et al., 1998; Wilson et al., 1998). Although we aimed for four outcome assessments in total, we had a significant drop-out rate at 9 months (only 12 patients were available at 9 months, and 11 patients at 12 months). Thus, we restricted our analyses to the first two outcome assessments (i.e., 3 and 6 months) to maximise power. GOSE produces a score between 1-8 which describes the patients level of recovery, from death to full recovery (1 = death; 2 = vegetative state/unresponsive wakefulness syndrome; 3 = lower severe disability; 4 = upper severe disability; 5 = lower moderate disability; 6 = upper moderate disability; 7 = lower good recovery; and 8 = upper good recovery). All outcome assessors were blind to the patients’ EEG results. The GOSE scores were normalised using a rank-based inverse Gaussian method.

3.3.7 Linear Regression Modeling

To determine the prognostic potential of HEPs, we conducted a multiple linear regression analysis, with GOSE score as the dependent variable (separately at each follow-up time point of three and six months). To deal with the multidimensional structure of the HEP, we computed separate linear regressions for each HEP time point 0-450ms post-R, with four additional stationary regressors describing patient characteristics: age at the time of injury, Glasgow Coma Scale (GCS) score at the time of EEG, days since injury at the time of EEG and CT grade (see Table 3). We clustered significant time windows and summed the t-values in each cluster. If a positive cluster persisted, we generated a null distribution by shuffling the GOSE scores and recomputing the multiple linear regressions at each time point, saving the t-sum of the largest cluster. This was repeated with 200 permutations. Finally, significant clusters with respect to the null distribution were stored.

We also performed a multiple linear regression with HEP variance computed across 0-450ms (replacing HEP amplitude), with the patient characteristic regressors: age at the time of injury, Glasgow Coma Scale (GCS) score at the time of EEG, days since injury at the time of EEG and CT grade.

3.3.8 Control ECG analyses

We conducted control analyses on the ECG to ensure cardiac activity did not contribute to the neural HEP effects. Thus, we conducted equivalent ECG regression analyses to those performed on the HEPs.

Additionally, we performed multiple linear regressions on heart rate and heart rate variability separately (replacing the HEP regressor), with the patient characteristic regressors: age at the time of injury, Glasgow Coma Scale (GCS) score at the time of EEG, days since injury at the time of EEG and CT grade. Due to time constraints, we could not correct all R-peak detection errors from the long continuous rest ECG recording (unlike our thoroughly corrected R-peak detection for the HEPs). Thus, we calculated heart rate as the trimmed mean (10%) of the R-R intervals and heart rate variability as the standard deviation of the R-R intervals after 10% of the extremes rejected. In the future, we will select a shorter time window to conduct precise R-peak detection, calculating heart rate and heart rate variability more accurately.

3.4 Results

3.4.1 Linear regression modelling

3.4.1.1 HEP amplitude

At three months post-EEG, multiple linear regression analysis indicated that HEP amplitude at centrofrontal electrodes did not significantly predict GOSE outcome from an unresponsive state (no positive clusters).

At six months, multiple linear regression analysis indicated that HEP amplitude at 211ms significantly predicted GOSE outcome from an unresponsive state ($p = 0.049$, standardized beta (SE) = 0.445 (0.199), unstandardized regression coefficient (SE) = 0.617 (0.276)) (see Figure 16). Furthermore, GCS at the time of EEG also significantly predicted GOSE at six months ($p = 0.048$, standardized beta (SE) = 0.544 (0.242), unstandardized regression coefficient (SE) = 0.194 (0.086)). All other predictors were not significant (smallest $p = 0.206$). The overall model, including average HEP amplitude at centrofrontal electrodes, age at the time of injury, GCS at the time of EEG, days since injury (at the time of EEG), and CT grade, did not significantly predict six-month GOSE outcome (F (5,10) = 3.157, $p = 0.058$, Adjusted $R^2 = 42\%$). It should be noted that the significant HEP effect is at a single time point with marginal significance. Therefore, it is highly likely that this result is due to chance. Despite this, the HEP effect persisted with the rejection of one patient who was withdrawn from life-sustaining treatment whose cause of death was ambiguous (207-223ms, $p = 0.043$, standardized beta (SE) = 0.469 (0.192), unstandardized regression coefficient (SE) = 0.955 (0.388)).

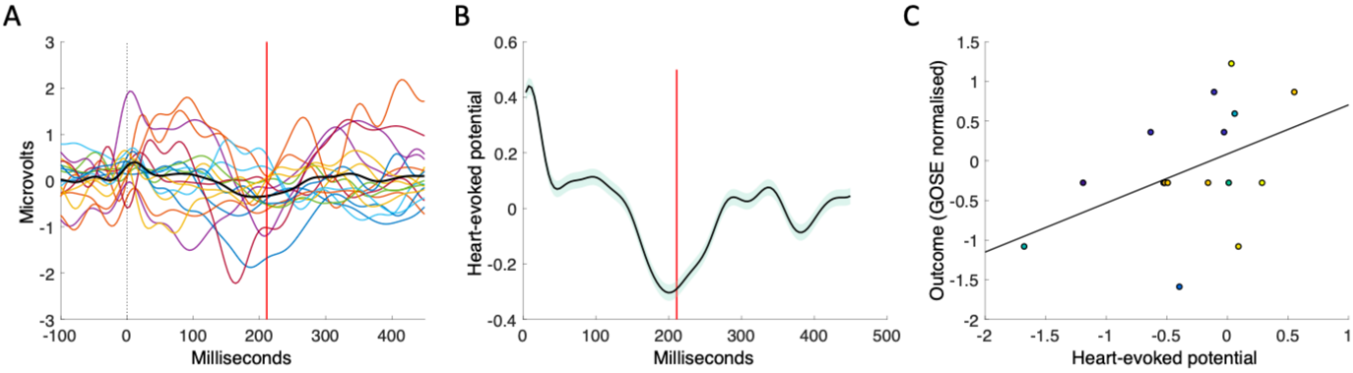


__Figure 16.__ [A] Averaged centrofrontal heart-evoked potential of each patient, black line indicates averaged heart-evoked potential across the group, and red vertical line indicates the significant time-point of the predictive effect of six-month outcome (i.e., 211ms). [B] Close-up of all patients' averaged centrofrontal heart-evoked potential with blue shaded 95% confidence interval and red vertical line indicating the significant regression time-point of six-month outcome. [C] Correlation of outcome at six months (normalised Glasgow Outcome Scale Extended (GOSE) scores) with average centrofrontal heart-evoked potential at the significant regression time-window (i.e., 211ms – red vertical line in A and B).

3.1.1.1 HEP variance

HEP variance across 0-450ms post-R did not significantly predict recovery from unresponsiveness at three and six months (smallest $p = 0.829$).

3.1.1.2 Control results

3.1.1.3 ECG

ECG amplitude significantly predicted 3-month GOSE outcome 406-445ms post-R (*p* = 0.017, standardized beta (SE) = 0.635 (0.017), unstandardized regression coefficient (SE) = 0.019 (0.007)). The overall model including ECG, age at the time of injury, GCS at the time of EEG, days since injury (at the time of EEG), and CT grade, significantly predicted 3-month outcome (F (5,11) = 5.612, *p* = 0.010, Adjusted R^2 = 58%). Furthermore, ECG significantly predicted 6-month GOSE outcome 426-438ms post-R (*p* = 0.041, standardized beta (SE) = 0.633 (0.270), unstandardized regression coefficient (SE) = 0.014 (0.006)). The overall model including ECG, age at the time of injury, GCS at the time of EEG, days since injury (at the time of EEG), and CT grade, significantly predicted 6-month outcome (F (5,10) = 3.322, *p* = 0.050, Adjusted R^2 = 44%). However, it should be noted that both ECG results are not significant when rejecting one patient who was withdrawn from life-sustaining treatment (no positive clusters).

3.1.1.1 Heart rate & heart rate variability

Heart rate or heart rate variability did not significantly predict GOSE outcome at 3 or 6 months (smallest *p* = 0.254).

3.1.1.2 Without CFA correction

To ensure the HEP regression effects were not a result of artefactual differences in CFA correction, we performed equivalent analyses on HEPs without CFA correction. HEPs without CFA correction did not significantly predict GOSE outcome at three or six months (no positive clusters). Therefore, the reported HEP effect may be due to artefacts induced by CFA correction.

3.2 Discussion

Embodied cognition frameworks describe the body as an essential component of cognition and consciousness (Craig, 2009; A. Damasio, 2010; Seth, 2013; Seth & Friston, 2016). Supporting these frameworks, an abundance of evidence demonstrates the key role of internal bodily signals for self-related aspects of awareness (Azzalini et al., 2019; Critchley & Garfinkel, 2018). In particular, the visceral milieu contributes to pre-reflexive/minimal forms of selfhood, which characterise the sense of 'mineness' and a unified first-person perspective of subjective experience (Gallagher, 2005; Limanowski & Blankenburg, 2013; Park & Tallon-Baudry, 2014). Thus, we expected brain-viscera markers to provide an avenue for detecting self-cognitive aspects of conscious experience. Indeed, previous research has demonstrated the role of cortical signatures of cardiac processing (i.e., HEPs) in self-cognition (Babo-Rebelo et al., 2016, 2019; Park et al., 2016, 2017, 2018) and in chronic disorder of consciousness diagnoses (Candia-Rivera et al., 2021; Raimondo et al., 2017). Therefore, as in previous research (Candia-Rivera et al., 2021; Raimondo et al., 2017), we expected the HEPs of conscious patients (although unresponsive) to be distinguished from unconscious patients and for this to be translated into a better functional outcome (Edlow et al., 2021). This is considering similar rates of covert cognition have been detected in acute unresponsive patients as in chronic patients (Claassen et al., 2019). Moreover, we also expected HEPs to provide valuable prognostic information in unconscious patients by distinguishing between those with preserved and dysfunctional residual internal network functioning (i.e., just as with early external sensory responses (Carter & Butt, 2005; Tsubokawa et al., 1980)). Thus, we expected those with HEPs demonstrating intact internal networks to be more likely to recover associated self-cognitive processes than those with HEPs reflecting dysfunctional internal networks. Hence, we hypothesised HEPs to provide a graded prediction of outcome from unresponsiveness: with those with highest conscious HEP amplitudes to be most likely to functionally recover, followed by those unconscious but with preserved internal network functioning, and lastly, those unconscious with dysfunctional network functioning with a worst expected recovery. Finally, cardiac measures such as heart rate and heart rate variability reflect the integrity of descending brain-heart pathways (McCraty & Shaffer, 2015). Thus, we also hypothesised cardiac measures to be predictive of consciousness recovery from acute unresponsiveness.

However, in contradiction to our hypotheses, we didn't find convincing evidence of a relationship of HEP amplitude or variance across time with recovery from an unresponsive state. Specifically, we observed a single time-point of HEP amplitude (211ms post-R) which significantly predicted outcome at six months post-assessment. However, considering this result is a single time point with marginal significance of $p = 0.049$, this result is likely due to chance. Furthermore, without CFA correction, this result does not persist, suggesting this effect may result from differences induced by ICA CFA correction. CFA correction is important to ensure HEPs reflect neuronal processing of cardiac activity rather than the cardiac activity itself (Kern et al., 2013). Furthermore, CFA correction diminishes the insertion of artefactual differences in HEP effects. For example, differences in the CFA across individuals or conditions can be reflected as artefactual HEP differences if the CFA is not corrected sufficiently (Azzalini et al., 2019). Conversely, CFA correction can insert artefactual differences if CFA influences are attenuated differently in some individuals or conditions than others. The problem of appropriate CFA correction is accentuated by the lack of standardised preprocessing and analysis HEP procedures (Coll et al., 2021a; Park & Blanke, 2019). Possible CFA-correction methods include ICA, rest template or nose recording subtraction, Hjorth source derivation, current source density transformation, and time-window selection with minimal CFA-influences (most using R-peak+455-595ms), as well parallel control analyses on cardiac measures (Coll et al., 2021a). Considering the variability of the appropriate CFA correction method and uncertainty of the adequacy of CFA reduction, control analyses with and without CFA correction are essential to ensure the correction method does not insert artificial effects. In this case, our HEP result is present with CFA correction but does not persist without, suggesting the result may be an artefact of the CFA correction method. Alternatively, the CFA may obscure the influence of the HEP on outcome from unresponsiveness, but unfortunately, which is the case is difficult to determine.

The lack of predictive HEP recovery effects is inconsistent with previous diagnostic research, which indicates HEPs distinguish between chronic consciousness state diagnoses with high accuracy (Candia-Rivera et al., 2021; Raimondo et al., 2017). These findings are compatible with our prediction of covert consciousness being present in some of our acute unresponsive patients and for this to be translated to a better functional recovery (Claassen et al., 2019; Edlow et al., 2021). However, it may be that our patients were unconscious at the time of HEP recording and that HEPs indicate the presence of consciousness but do not prospectively predict its recovery. For example, it could be that interoceptive self-cognitive processing (reflected in HEPs) is active when consciousness is present, but these mechanisms are absent during unconsciousness. Indeed, HEP amplitude reduces with sleep depth but increases similarity with wakefulness during REM sleep (Lechinger et al., 2015; Simor et al., 2021). This suggests when unconscious, HEP interoceptive mechanisms which contribute towards subjective experience are substantially reduced. Furthermore, we also predicted HEPs during unconsciousness to predict recovery of self-cognitive processes by determining the preservation of internal self-related networks. Nevertheless, in contradiction to our hypotheses, our findings suggest HEPs do not predict outcome from unresponsiveness, and therefore potentially do not indicate the preservation of internal networks.

Furthermore, we didn’t observe evidence of the prognostic value of cardiac measures in unresponsive patients. Specifically, heart rate and heart rate variability did not predict consciousness outcome at three or six months. This contrasts with our prediction of these measures demonstrating the integrity of descending brain-heart pathways and thus predicting the recovery of associated processes. Previous research provides inconsistent evidence of the relationship of cardiac measures with consciousness diagnoses. For example, consistent with our findings, Candia-Rivera et al (2021) and Raimondo et al (2017) found no significant heart rate or heart rate variability differences between chronic consciousness state patient diagnoses, using both time and frequency domain measures. However, a substantial line of research has highlighted the utility of heart rate variability for consciousness diagnosis and prognosis (Leo et al., 2016; Riganello et al., 2010, 2011, 2012, 2015, 2018, 2019; Tobaldini et al., 2018). Nonetheless, a large proportion of those studies involved noxious or emotional stimulation instead of resting-state. Thus, implementing an emotional or self-processing task may improve the predictive power of cardiac measures on consciousness recovery. Due to time constraints, we computed a simple time-domain measure of heart rate variability (i.e., the standard deviation of all sinus beats (SDRR), once rejecting 10% of outliers). Previous research has observed spectral measures to indicate autonomic dysfunction (i.e., reduced LF/HF ratios), and for this to be associated with poor outcome and an increased risk of brain death (Biswas et al., 2000). Furthermore, mathematical chaos may better characterise heart rate variability due to its complex fluctuations over large time scales. Thus, future research could adopt spectral or non-linear complexity heart rate variability measures to gauge better its relationship with consciousness (Riganello et al., 2018). Finally, five patients had sinus tachycardia characterised as a sinus rhythm faster than the range considered normal (Olshansky & Sullivan, 2013). A consistently faster heart rate can influence heart rate variability by constraining the variability to low values (Dhananjay & Sivaraman, 2021). We included these patients in the cardiac measure analyses as this condition could contribute towards outcome from unresponsiveness, although usually considered benign (Olshansky & Sullivan, 2013; Shabtaie et al., 2020). We ensured to control for faster rhythms in the HEP analyses by restricting our analysis window to 0-450ms, ensuring no contaminating additional heartbeats in the HEP analysis window.

We observed a late ECG effect (406-445ms post-R) predictive of outcome from unresponsiveness at three and six months. For the majority of the patients (i.e., 15), their averaged ECG at this time reflected diastole (i.e., cardiac relaxation). Thus, low-level cardiac information may provide prognostic value of recovery from unresponsiveness, potentially by demonstrating healthy cardiac functioning during cardiac relaxation. However, for one patient, this time window reflected the QRS complex of the next heartbeat (i.e., sinus tachycardia), and for another patient, this was during premature ventricular contraction (Gliner et al., 2018). The patient with premature ventricular contraction had an outcome of death, and the patient with very fast sinus tachycardia had an outcome of lower severe disability. We initially included these patients in the analysis, as these cardiac conditions may contribute towards outcome. Indeed, individuals with >12 premature ventricular complexes per day have an increased risk of cardiac death (Lin et al., 2017), although sinus tachycardia is typically benign (Olshansky & Sullivan, 2013; Shabtaie et al., 2020).

However, the ECG predictive effect did not survive the rejection of one patient who was withdrawn from life-sustaining treatment (i.e., the patient with premature ventricular contraction). Death from withdrawal is a difficult outcome to interpret, as their death is not a result of natural circumstances. For example, this patient may have recovered if not withdrawn from life-sustaining treatment. Furthermore, the reason for withdrawal is unknown and may not result from unhealthy cardiac functioning, but a result of dysfunction of a different organ system etc. This concern also corresponds to patients with an outcome of death, as the cause of death is often uncertain (although in our study, we only have one patient who died – which was from withdrawal). Thus, the relation of their ECG and outcome is ambiguous, so a control analysis with the rejection of those with an outcome of death or withdrawal is necessary. Finally, as mentioned, five patients had a faster rhythm than average (i.e., sinus tachycardia), and two patients demonstrated occasional premature ventricular contractions. Future research with a larger sample could reject these patients with cardiac abnormalities, but this was not possible with our small sample.

Not surprisingly, our behavioural index of consciousness (i.e., GCS) significantly predicted six-month outcome from unresponsiveness at the time of the significant predictive HEP effect (i.e., 211ms). Although behavioural consciousness markers indicate cognitive functioning in some patients, there are high misdiagnosis rates for patients without or with limited voluntary behavioural control (Andrews et al., 1996; Childs et al., 1993; Schnakers, Vanhaudenhuyse, et al., 2009b). Indeed, cognitive motor dissociation patients are behaviourally identified as unconscious but revealed to be conscious via their brain responses (Cruse et al., 2011; Edlow et al., 2021; Owen et al., 2006). Therefore, advanced neuroimaging techniques are imperative for accurate consciousness classification. Although there has been substantial progress with neuroimaging techniques analysing external perceptual aspects of awareness, less research has been conducted on internal self-related aspects of awareness (Vanhaudenhuyse et al., 2011). Future research is needed to refine internal self-awareness markers, potentially by analysing the integration of the brain with a variety of internal organs, such as via gastric-brain or respiratory-brain coupling (Heck et al., 2016, 2017; Rebollo et al., 2018, 2021; Zelano et al., 2016). Combining multiple neural markers has proven to be successful for consciousness diagnosis (Engemann et al., 2018; Raimondo et al., 2017; Sitt et al., 2014). Thus, a similar combined approach may enhance prognosis in the future, particularly by encompassing both internal and external awareness signatures

A significant limitation of our approach is the difficulty of ascertaining the level of consciousness of our acute unresponsive patients at the time of HEP recording. We completed the Glasgow Coma Scale (GCS) prior to electrophysiological recording. However, this scale is a rapid assessment recording limited behavioural responses. A more thorough and repetitive assessment of consciousness state, such as via the Coma Recovery Scale – Revised (CSR-R), may have revealed greater insight into the level of consciousness of these patients (Giacino et al., 2004). However, both diagnostic scales focus exclusively on assessing external perceptual aspects of awareness. For example, these scales assess auditory, visual, and noxious responses, which reflect awareness of the environment. Therefore, these scales do not assess internal self-related awareness processes (associated with HEPs), although assessing communication and command following may involve an aspect of self-cognition. Thus, future research could include assessments of self-awareness such as via the Self-Reflection and Insight Scale (SRIS) and the Self-Consciousness Scale-Revised (SCS-R) (Grant et al., 2002; Scheier & Carver, 1985). However, these methods assess consciousness behaviourally, which doesn't account for unresponsive patients with covert cognitive capabilities (Cruse, Gantner, et al., 2014; Edlow & Naccache, 2021). Therefore, assessing conscious neural responses independent of behavioural response may be more valuable for future research, such as those reflecting high-level language comprehension (Gui et al., 2020; Rohaut et al., 2015; Sokoliuk et al., 2019).

We aimed to investigate an important subset of patients who failed to follow commands after sedation, as these patients are most in need of accurate prognostication. Thus, we implemented moderately stringent inclusion/exclusion criteria to ensure we accurately sampled our target group. Unfortunately, this resulted in a reasonably small sample of 17 patients with low variability in consciousness outcomes. In fact, only three patients had poor outcome values of vegetative state/unresponsive wakefulness syndrome or death at three and six months, while the remaining patients recovered consciousness. Therefore, a larger cohort of patients with greater variability in consciousness outcome is needed to more accurately assess the contribution of HEPs, ECG, and cardiac measures to consciousness prognoses. Moreover, our outcome assessment was completed over the phone with a next of kin (or patient if recovered capacity), primarily focused on behavioural recovery. A more extensive repetitive in-person outcome assessment performed by a trained clinician may have provided a more detailed indication of the patients' cognitive capabilities. In particular, our interoceptive measures may have predicted emotional and self-cognitive abilities rather than broad behavioural recovery categories.

As described, it is hard to determine whether our lack of significant predictive effects was a result of the HEPs reflecting reduced or absent self-cognitive mechanisms, as we cannot ascertain the patients' consciousness state at the time of HEP recording. Thus, future research could focus on improving the assessments of the patients' consciousness state at the time of recording (via cognitive/neurological and more in-depth behavioural assessments). However, another suggested improvement could be to record HEPs during a task involving self-processing to more actively engage self-cognitive mechanisms. For example, patients could follow instructions involving imagining themselves from a first or third-person perspective, as this has previously been observed to modulate HEP amplitude (Babo-Rebelo et al., 2016, 2019). However, this task requires complex cognitive demands, which may be difficult for recently severely brain-injured patients. Thus, more passive self-cognitive tasks may be more appropriate such as comparing HEPs while they listen to their own voice in comparison to a familiar other's voice, or their own name, or self-engaging words (e.g., first-person vs third-person phrases). Furthermore, we predicted that HEPs would provide information on the preservation of internal networks. Alternatively, implementing a task involving interoceptive-exteroceptive integration, such as that described in Chapters 2-3, may more broadly assess the integrity and interaction of both modalities networks necessary for conscious selfhood (Banellis & Cruse, 2020, 2021). Furthermore, perturbatory methods such as vagus nerve stimulation (VNS) may provide more extensive evidence of the preservation of internal networks (Paciorek & Skora, 2020; Richter et al., 2021; Villani et al., 2019; Weng et al., 2021). For example, non-invasive transcutaneous auricular VNS was observed to increase heart rate variability, corresponding to frontal increases in the theta-band and delta-band, as well as more diverse influences on higher frequency bands in frontal and fronto-parietal areas (Machetanz et al., 2021). Thus, observing perturbatory EEG and ECG responses to non-invasive VNS may be a more promising method of assessing the responsiveness of internal networks.

In conclusion, we did not observe substantial evidence of the prognostic potential of HEPs or cardiac measures. One interpretation is interoceptive processing reflected in HEPs contributes towards self-consciousness only when conscious, but these mechanisms are significantly diminished when unconscious. Therefore, these interoceptive self-cognitive mechanisms are lacking in acute unresponsive patients, reflected in the absence of a relationship with consciousness prognosis. However, it is difficult to ascertain the state of consciousness of our patients due to limited behavioural assessments at the time of HEP recording. Thus, it is possible that some patients were conscious during HEP acquisition. Another possibility is that at rest, self-cognitive mechanisms in HEPs are much less prominent, and therefore, implementing self-processing tasks may reveal alternative HEP prognostic effects. Furthermore, we had a small sample with low variability in consciousness outcome. Thus, more research is needed with a larger multisite cohort of patients with a broader range of recovery outcomes. Finally, future research could investigate the integrity of interoceptive networks more broadly, potentially via vagus nerve stimulation, which could more accurately predict the recovery of high-level functioning of these networks (Paciorek & Skora, 2020).

CHAPTER 5: GENERAL DISCUSSION

This final chapter provides an overview and general discussion of the observations from experimental chapters 2-4. I first reiterate the key aims and motivation for this project, followed by a summary of the empirical findings, their interpretation, evaluation, application in disorders of consciousness, limitations, and, lastly, suggestions for future directions. Table 4 presents an overview of the main findings from chapter 2-4.

5.1 Research Questions and Rationale

In this thesis, I describe two experiments developed to characterise mechanisms of interoceptive-exteroceptive integration. In particular I sought to determine if these integrated mechanisms were compatible with the precision-weighting properties of predictive coding frameworks. Understanding the mechanistic account of interoceptive-exteroceptive integration is essential because it underlies broad perceptual and cognitive processes. Indeed integrating multimodal signals is necessary for perceiving and interacting with the external world via the body as an embodied self (Azzalini et al., 2019; Craig, 2009; Critchley & Garfinkel, 2018). Thus, shedding light on interoceptive-exteroceptive integration will enhance our understanding of broad aspects of cognition, including decision-making, action, embodied selfhood, emotional experience, and the first-person perspective.

In particular, integrated interoceptive processing is imperative for internal self-related aspects of awareness (Damasio, 2010; Salvato et al., 2020; Seth & Tsakiris, 2018). Indeed, selfhood can be viewed as the crux of conscious experience, as selfhood characterises the subject of subjective experience, the sense of 'mineness', the unified point of view in which consciousness arises, and the relation of experience to ourselves for valence, emotion, and cognitive reflection (Bortolan, 2020; Zahavi, 2008). Much of these self-processing dimensions express a pre-reflective minimal form of selfhood, such as the self-referential quality of subjective experience and sense of 'mineness' (Gallagher & Zahavi, 2012; Metzinger, 2003). Minimal selfhood is pre-reflective in the sense that it is non-observational, as the identification of experience as our own is independent of conceptualising the self and linguistically articulating about it (Bortolan, 2020; Gallagher & Zahavi, 2012). Furthermore, minimal selfhood is non-objectifying, as the self is characterised as the subject of subjective experience rather than an object. For instance, objects have a perceptual external existence with concrete boundaries viewed from multiple perspectives (or not at all), whereas there are no apparent external boundaries of selfhood (i.e., we do not define selfhood by the body's spatial arrangement of its organs), and it is perceived as 'the same old body always there' (James, 1890; Seth & Tsakiris, 2018). This more primitive pre-reflective self-awareness is thought to arise from a sense of embodiment, as the body acts as a vehicle for the self to perceive and interact with the world in a unified manner (Gallagher, 2005; Limanowski & Blankenburg, 2013). This minimal form of self is distinguished from the narrative self, a higher-level personal identity created from reflecting on experiences over time (Bortolan, 2020).

Despite minimal selfhood portraying an intrinsic feature of subjective experience, internal self-related aspects of awareness are under-assessed in patients with disorders of consciousness. The under-evaluation of self-awareness is especially concerning as the disorder of consciousness diagnostic criteria includes awareness of the self and the environment (Royal College of Physicians, 2020). However, current clinical standards rely on detecting external perceptual aspects of awareness of the environment. This bias towards external awareness may in part explain the high misdiagnosis rates in PDOC patients once re-assessed by experienced teams (Andrews, 1996; Childs et al., 1993; Schnakers, Perrin, et al., 2009). Including assessments that focus on internal self-related and external perceptual awareness ensures more facets of awareness are characterised and subsequently boost diagnostic and prognostic accuracy. Thus, we need more research on internal self-related aspects of awareness in disorder of consciousness patients. Furthermore, current diagnostic tests rely on behavioural methods of self-reporting conscious experiences. Consequently, behavioural assessments exclude the detection of covert cognitive capabilities in patients with motor impairments and fluctuations in vigilance. Therefore, neuroimaging methods independent of behavioural responses are preferable to ensure non-communicating patients aren't misdiagnosed.

In support of the embodied nature of minimal forms of selfhood, a wealth of research demonstrated the importance of interoceptive processing for self-awareness. For example, integrating cardiac signals into bodily illusions increases multiple aspects of self-processing. Specifically, pulsing a virtual limb or full-body in synchrony with the participants' heartbeat results in a greater sense of ownership of the phantom body, shifts the perceived location of self towards the false body, and increases identification with facial features of an others image (Aspell et al., 2013; Heydrich et al., 2018; Sel et al., 2017; Suzuki et al., 2013). Furthermore, individual's ability to sense their heartbeat modulates self-processing (Sel et al., 2017; Suzuki et al., 2013; Tajadura-Jiménez et al., 2012; Tsakiris & Critchley, 2016). Moreover, markers of cortical cardiac processing (i.e., heart-evoked potentials; HEPs) fluctuate with self-processing dimensions, bodily self-consciousness, self-recognition, and perceptual consciousness (Al et al., 2020; Babo-Rebelo et al., 2016, 2019; Park et al., 2017; Park et al., 2014, 2016). Most importantly, these HEP signatures differentiate between consciousness state diagnoses with high accuracy (Candia-Rivera et al., 2021; Raimondo et al., 2017). Thus, in a final experimental chapter, I describe a prognostic study to predict the recovery of self-awareness from acute unresponsive states, using neural signatures of interoceptive processing (i.e., heart-evoked potentials). This method is advantageous as it is independent of behavioural response and characterises embodied self-awareness - an under-assessed but critical component of the diagnosis criteria. Crucially, the evaluation of consciousness remains one of the most vital challenges of modern medicine. The impact on patients, caregivers, and clinicians is immense, as accurate prognoses implicate critical care decisions such as rehabilitation assignments and life-sustaining treatment decisions.

5.2 Summary of Findings

Table 4. *Overview of the main experimental findings from chapters 2-4. Definitions: 'pre-omiss' = pre-omission ERP effects locked to the heartbeat (i.e., HEPs), 'post-omiss' = ERP effects locked to the omission (i.e., omission responses), 'ME' = main effect.*

	Chapter 2	**Chapter 3**	**Chapter 4**
Topic	Signatures of interoceptive-exteroceptive integration	As Chapter 2 – with individually-tailored timing of heartbeat perception	Prognostic potential of resting HEPs in acute unresponsive patients
Behavioural results			
Summary of findings	- Interoceptive and exteroceptive performance above chance at group level.	- Part 1: 8/34 high heartbeat perceivers - Part 2: above chance performance at group level (but weak interoceptive Bayesian evidence) - Chapter 3-Part 2 performance not significantly better than Chapter 2	- N/A
Electroencephalography results			
Summary of findings	- *Pre-omiss ME delay*: HEP evidence of cardiac-driven expectations of sounds (R+93-169ms) - *Post-omiss attention x delay interaction*: Attention modulated predictive mechanisms (delay difference internal attention only) (Omiss+95-138ms) - No significant influence of interoceptive ability	- *Pre-omiss ME delay*: HEP evidence of cardiac-driven expectations of sounds (R+79-128ms) - *Post-omiss ME delay*: integrated predictive mechanisms present (Omiss+94-137ms) - No significant attention modulation of predictive mechanisms (no attention x delay interaction) - *Pre*-omiss ME attention (R+37-68ms) - No significant interoceptive ability	- HEP amplitude & variance not significantly predictive of 3-month outcome from unresponsiveness - HEP amplitude (R+211ms) predictive of 6-month outcome from unresponsiveness (all other time points and variance not significant)

		modulation of predictive mechanisms (no ability x delay interaction) - *Post-omiss interoceptive awareness x attention interaction (synch trials)*: attention difference high awareness only (Omiss+96-139ms)	
Electrocardiography results			
Summary of findings	- No significant ECG differences - IBI's sig longer internal than external attention - IBI cardiac deceleration following omission external trials only - HRV sig more variable internal than external attention (but weak Bayesian evidence)	- No significant ECG differences - IBI's sig longer internal than external attention - IBI cardiac deceleration following omission external trials only - No significant HRV differences	- ECG predictive of 3-month (R+406-445ms) & 6-month outcome (R+426-438ms) from unresponsiveness - Heart rate & HRV not significantly predictive of outcome

5.2.1 Chapter 2: Signatures of Interoceptive-Exteroceptive Integration

The research in Chapter 2 was motivated by a previous study that indicated the brain integrates cardiac signals to predict auditory stimuli (i.e., interoceptive-exteroceptive integration) (Pfeiffer & De Lucia, 2017). We aimed to replicate evidence of interoceptive-exteroceptive predictions and investigate whether state and trait measures of precision (i.e., attention and individual differences in interoceptive ability) modulate these cross-modal mechanisms. This chapter found evidence of cardiac-driven expectations of sounds (as in Pfeiffer & De Lucia., 2017), reflected as a HEP pre-omission difference across short and long cardio-audio delay trials. Furthermore, we observed modulation of these integrated predictive mechanisms by attentional precision, evidenced as a post-omission difference across delay conditions when focusing internally only (we observed no delay difference when attending externally). Despite observing evidence of state precision modulation, we found no evidence of trait precision modulation by interoceptive ability. Thus, our interoceptive-exteroceptive integration findings are in partial support of predictive coding frameworks. However, the lack of trait precision modulation of predictive responses is incompatible with precision-weighting properties described by these predictive coding accounts.

5.2.2 Chapter 3: Individual-Tailored Heartbeat Perception Timing

Chapter 3's research was motivated to address the inconsistent evidence of the influence of precision on predictive mechanisms in Chapter 2 (i.e., a significant effect of state precision but not trait precision). Specifically, we tested whether the lack of trait precision modulation resulted from inaccurate measurements of interoceptive performance due to individual differences in the perceived timing of heartbeat sensations. Thus, we tailored the cardio-audio delays to reflect each individual's preferred time of perceived synchrony to more accurately determine the influence of trait precision on cross-modal predictive mechanisms. Despite implementing a more fine-tuned paradigm for detecting trait precisional differences, we did not observe evidence of modulation of predictive mechanisms by interoceptive ability. Furthermore, we did not replicate evidence of state precision modulation of integrated cross-modal predictive mechanisms by attention. Nonetheless, we did replicate evidence of heartbeat-driven expectations of sounds from Chapter 2 (i.e., pre-omission delay effect), as well as observing preserved post-omission mechanisms of integrated predictive mechanisms. Therefore, under a more precise individually-tailored paradigm, interoceptive-exteroceptive integration does not function in a precision-weighted predictive manner.

5.2.3 Chapter 4: Prognostic Potential of Resting HEPs from Unresponsiveness

The work presented in Chapter 4 was motivated by a lack of prognostic research on self-related aspects of awareness in disorders of consciousness patients. Given the role of interoception in embodied selfhood, we aimed to determine if resting heart-evoked potentials (i.e., a cortical signature of interoceptive processing) provide prognostic utility for predicting the recovery of self-awareness from acute unresponsive states (Azzalini et al., 2019; Critchley & Garfinkel, 2018; Seth, 2013; Seth & Tsakiris, 2018). Although previous evidence indicated HEPs provided diagnostic value in prolonged disorders of consciousness, we observed no prognostic potential of resting HEPs in acute unresponsive patients (Candia-Rivera et al., 2021; Raimondo et al., 2017). However, a larger sample with greater variability in outcome and more in-depth consciousness assessments at recording is necessary to confirm the prognostic value of HEPs.

5.3 Interpretation

5.3.1 Cardio-audio expectation

The experimental findings of Chapters 2-3 indicate that interoceptive-exteroceptive integration operates partially according to interoceptive predictive coding frameworks. Indeed, in both experiments, we observed robust evidence of heartbeat-driven expectations of sounds.

This cardio-audio expectation effect was depicted as a HEP difference when comparing pre-omission periods embedded in perceived synchronous sound sequences with the heartbeat (sounds short delay from heartbeat) with pre-omission periods in perceived asynchronous sound sequences (sounds long delay from heartbeat). This HEP difference across cardio-audio delay trials reflected qualitatively distinct topographic distributions, suggesting the cardio-audio delay generates different neural mechanisms of cardio-audio expectation. Furthermore, the pre-omission HEP in short delay trials gradually drifted upwards as expectation builds, similar to the contingent negative variation potential (CNV) known to reflect changes in expectations (Chennu et al., 2013) (see Figure 5 and Figure 12). This suggests that presenting sounds at different delays from the heartbeat induces different expectations of sounds, highlighting the brains' ability to use cardiac signals to predict auditory stimuli. It may be that presenting sounds at a delay close to the heartbeat (i.e., perceived as synchronous) enables a cardio-audio prediction to be sustained, but a cardio-audio prediction cannot be sustained over a long delay not perceived as synchronous. Alternatively, perceived synchrony may directly result from the fulfilment of cardio-audio expectation, which could be at a longer delay for some individuals. Whether a short delay or perceived synchrony (i.e., at varying delays) is more important for a cardio-audio expectation is difficult to ascertain. This is because the effect is present in both Chapter 2, which has fixed delays (i.e., less focused on individual perceived synchrony), and Chapter 3, which has individually-adjusted variable delays (i.e., more focused on individual perceived synchrony). Thus, in this thesis, the effect of perceived synchrony and cardio-audio delay is impossible to separate. Future research could compare participants with longer perceived synchronous cardio-audio delays with a shorter perceived asynchronous delay to determine whether perceived synchrony or the cardio-audio delay has more influence on cardio-audio expectation.

The cardio-audio expectation effect observed in Chapters 2-3 is consistent with research by Pfeiffer & De Lucia et al (2017), who observed a similar HEP difference during omissions when comparing cardio-audio synchronous trials with asynchronous trials (Pfeiffer & De Lucia, 2017). The authors interpret this effect as a prediction error signal from predicting a sound to occur at the heartbeat in synchronous trials. Consequently, the lack of a cardio-audio synchronous sound (i.e., omission) generates a surprise or prediction error response. Thus, these findings further support the existence of integrated cardiac-auditory predictive mechanisms. However, in that study, it is impossible to separate the auditory omission response from the prediction error response as both responses are time-locked to the heartbeat in synchronous trials. But the omission-response has a variable onset with respect to the heartbeat in asynchronous trials. Thus, the auditory omission response is a confound in that study, whereas in our study, we avoid this confound by implementing cardio-audio delays that weren't variable for both perceived synchronous and perceived asynchronous trials (for each individual). This is also advantageous as it allowed us to analyse pre-omission expectation and post-omission unfulfilled expectation responses separately.

Some interpret post-omission responses to similarly reflect top-down expectation, as in pre-omission responses. This is because prediction error is proposed to be calculated by an inhibitory pulse that 'subtracts' expectation from sensory input signals (Heilbron & Chait, 2018; Wacongne et al., 2012). Therefore, as there is no sensory input to 'subtract' during omissions, post-omission responses may reflect pure top-down predictive signals. Alternatively, it is possible omission responses could represent prediction error if a memory template is subtracted from predictive signals (instead of sensory input). However, Bendixen et al (2009) demonstrated omission responses were present only when a second tone was omitted, not the first, suggesting a memory template was not implemented to generate the omission response. Nevertheless, that study only analysed very short latencies of <50ms. Thus, an omission response to the first sound could have been observed at a later latency. Therefore, as it is ambiguous whether omission responses reflect expectation or prediction error, we broadly refer to our post-omission effects as unfulfilled expectation responses.

van Elk et al (2014) completed a similar study by presenting sounds at different delays from the heartbeat (Rpeak+0ms, +100ms, +200ms, +300ms, +400ms, +500ms) and compared the auditory N1 response to the sounds across the cardio-audio delays. Without correcting for the cardiac field artefact (CFA), there was a significant effect of delay on the auditory N1 response. However, once applying CFA correction by subtracting a baseline condition in which no sound was presented, the delay effect was no longer significant. Therefore, in that study, the N1 difference across delay conditions likely reflected underlying CFA influences. Nevertheless, the N1 effect may be highly correlated with the CFA, and thus, correction diminished the N1 effect of interest. The lack of N1 differences across cardio-audio delay conditions in van Elk's study is consistent with our lack of observed auditory evoked potential (AEP) differences across delay conditions when including all participants in Chapter 3. However, when separating participants according to their interoceptive ability, we observed AEP differences in high heartbeat perceivers. Therefore, the lack of AEP (i.e., N1) delay difference after CFA correction in van Elk's study may result from poor heartbeat perceivers whose cardio-audio integrated mechanisms are weak. Despite this, when collapsing all heartbeat-delay conditions into a general heartbeat-related condition (and therefore increasing power), they found an N1 suppression to heartbeat-locked sounds compared to externally generated sounds unrelated to the heartbeat. This could be interpreted as heartbeat-related sounds reflecting less prediction error than non-heartbeat-related, as the brain uses the heartbeat to predict the sounds. However, with CFA correction, this effect is only marginally significant (*p* = .07). Our pre-omission HEP delay effect persists with CFA correction of the same method as this study (rest template subtraction in Chapter 2). Thus, we can conclude our results are not due to residual differences in cardiac activity, and therefore, likely reflect cardio-audio predictive mechanisms.

Control analyses from both experiments revealed a greater HEP difference between delay conditions before the fourth sound of each trial than before the first (i.e., before any sounds). This may reflect expectations building as more heartbeat-locked sounds are presented. However, it should be noted that a difference was present before the first sound despite no sounds being presented yet. This demonstrates the potential presence of residual CFA differences, despite applying correction methods. The topography of the pre-fourth sound delay difference is very similar to the pre-omission delay effect, whereas the pre-first sound topography is qualitatively distinct to the pre-omission effect, suggesting they are driven by different sources. Thus, the pre-fourth delay effect is likely to reflect cardio-audio expectation, similar to the pre-omission response. We interpret the pre-first sound delay effect to represent CFA influences (see 'Limitations of HEPs' section for discussion of CFA correction methods).

The cardio-audio expectation effect demonstrates that interoceptive-exteroceptive integration can function predictively, supporting interoceptive predictive coding frameworks. These frameworks suggest that embodied selfhood, emotional experience, and other high-level cognitive processes emerge from integrated predictive mechanisms across interoceptive, exteroceptive, and proprioceptive domains. Although our experimental findings are much simpler than the complex interplay of predictive mechanisms across all modalities, our results support the existence of predictive interoceptive and exteroceptive signals. Seth's interoceptive predictive coding framework emphasises the anterior insula cortex (AIC) as a core region for interoceptive predictive mechanisms. Specifically, Seth suggests the insula as important for interoceptive-exteroceptive integration and generating interoceptive prediction error via comparisons of interoceptive predictions with interoceptive signals (Seth, 2013). However, our source estimation did not reveal the insula from our cardio-audio predictive results (i.e., pre-omission or post-omission delay effects). This is inconsistent with a study demonstrating the anterior insular cortex as an important region for interoceptive-exteroceptive integration when comparing fMRI activity across cardio-visual synchronous and asynchronous streams (Salomon et al., 2016, 2018). However, the previous study implemented fMRI, which has greater spatial resolution than EEG source localisation. It may be that the insula is particularly difficult to detect with EEG source localisation as it is situated deeper in the brain. Thus, electrical activity from the insula may be attenuated on the brain's surface (Fahimi Hnazaee et al., 2020). Future research could investigate the neural regions involved in cardio-audio predictive mechanisms by employing the paradigm in Chapters 2-3 with fMRI.

The Embodied Predictive Interoceptive Coding (EPIC) describes the orbitofrontal and ventromedial prefrontal cortex as the highest regions of the interoceptive predictive network, supported by previous interoceptive research (Barrett & Simmons, 2015; Critchley & Harrison, 2013; Quadt et al., 2018). Subsequently, we expected these prefrontal regions to be active during cardio-audio expectation. However, we observe slightly different regions: the dorsolateral prefrontal cortex and anterior prefrontal cortex (which overlap with the ventromedial prefrontal cortex (Ramnani & Owen, 2004)). Thus, our prefrontal source estimates are broadly consistent with the EPIC model, which describe the generation of interoceptive predictions from agranular frontal regions. This is broadly consistent with previous research using cardiac attention tasks, although usually the inferior or middle frontal gyrus (Critchley et al., 2004; Kuehn et al., 2016; Pollatos et al., 2007; S. M. Schulz, 2016; Simmons et al., 2013; Wiebking et al., 2010; Zaki et al., 2012). However, our paradigm is more complex than unimodal interoceptive predictive models. Indeed, our paradigm includes auditory predictive mechanisms guided by interoceptive signals, which explains our temporal cortex activation. Models of auditory predictions during omission periods suggest auditory expectations arise from the inferior frontal gyrus (Chennu et al., 2016). Thus, perhaps different frontal regions with connections from both interoceptive and exteroceptive frontal areas, such as the dorsolateral prefrontal cortex, are activated for an integrated interoceptive-exteroceptive prediction.

As well as broad frontal regions, the supramarginal gyrus and middle temporal gyrus were consistently activated in the delay contrasts from Chapters 2-3 (except in the post-omission delay effect in Chapter 3). This suggests these regions play a particular role in cardiac-auditory integrated predictive mechanisms. Indeed, the supramarginal gyrus is activated during multisensory integration of internal and external signals from the body and environment during various interoceptive attention tasks (Nejad et al., 2015; Reichenbach et al., 2011; Salvato et al., 2020). Finally, there are some discrepancies between source estimates from Chapters 2 and 3: with Chapter 2 revealing somatosensory and motor regions, whereas Chapter 3 estimating visual and fusiform areas. It could be that implementing tailored delays in Chapter 2 enhanced heartbeat-driven expectations in more participants, as supported by the trend for better objective performance. Thus, source estimates from Chapter 2 more accurately reflect cross-modal expectations and subsequent predictive sources. However, future research could implement our paradigm with a technique of higher spatial resolution, such as fMRI, to more accurately investigate the neural mechanisms underlying cross-modal predictive mechanisms.

5.3.2 State Precision Modulation

Predictive coding accounts include a fundamental component known as precision-weighting, responsible for modulating predictive mechanisms (Friston, 2009, 2010). The weight of prediction error signals determines the relative importance of predictive signals both within and between modalities. This is formally presented as the inverse of the variance of probability distributions and thus, represents the uncertainty of the signal. Attention is described as a method of precision optimisation (Hohwy, 2012). Specifically, attending to a specific sensory channel is thought to fine-tune the precision of associated priors and prediction errors. Attention optimises precision by increasing model updating of that sensory modality, thus, over time, priors become more precise. However, models may need further updating if precise contradictory prediction errors emerge (Ainley et al., 2016; Hohwy, 2012). Therefore, attention will gradually ensure that predictive models precisely reflect sensory signals from the external world and the internal body.

We aimed to determine if integrated interoceptive-exteroceptive predictive mechanisms are modulated by state precision measures (i.e., attention) under precision-weighting properties of predictive coding. We tested this in Chapters 2-3 by manipulating attention. Half the time, participants focused on the synchrony of heartbeat sensations with auditory stimuli (i.e., internal attention). In the other half, participants focused on the rhythmicity of the sounds alone (i.e., external attention). In Chapter 2, we observed evidence of attentional-modulation of cardio-audio predictive mechanisms. This effect was demonstrated as an interaction of attention, and cardio-audio delay on post-omission evoked responses (i.e., omission-evoked potentials). Specifically, during internal attention, we observed a larger positivity to omissions within short delay cardio-audio sequences than long delay sequences, while no delay difference was observed during external attention. This suggests, with internal attention, there are stronger unfulfilled expectations of a sound when presented at a short perceived synchronous delay from the heartbeat than a long perceived asynchronous delay. Thus, Chapter 2's findings support the role of attentional state precision in modulating cardio-audio predictive mechanisms, supporting predictive coding frameworks (Ainley et al., 2016; Feldman & Friston, 2010a; Hohwy, 2012).

The attentional modulation of integrated cardio-auditory responses is consistent with research highlighting enhanced auditory predictive responses with attention (i.e., omission responses, mismatch negativity responses, and P300 responses) (Chennu et al., 2013, 2016; Garrido et al., 2009; Raij et al., 1997). Furthermore, attention modulates interoceptive heart-evoked potential responses (García-Cordero et al., 2017; Montoya et al., 1993; Petzschner et al., 2019; Schandry et al., 1986; Villena-González et al., 2017; Yuan et al., 2007). Thus, our cardio-audio integrated predictive mechanisms are consistent with previous research, demonstrating attentional modulation of separate auditory and cardiac responses. Critchley et al (2004) found comparable fMRI results of attentional modulation of cardio-audio integrated mechanisms. Indeed, Critchley also observed a larger difference between fMRI activity of cardio-audio delay conditions when internally attending than when externally focused. This was reflected as increased activity in the frontal operculum and insula, dorsal and medial parietal lobe, right dorsolateral prefrontal cortex, dorsal cingulate, and lateral temporal cortices when attending internally, in comparison to external attention. This overlaps approximately with our source reconstruction results of the attention and delay interaction in the right inferior frontal gyrus, bilateral supramarginal gyrus, and middle temporal cortex.

Despite observing evidence of modulation by attentional precision in Chapter 2, we didn't replicate this effect in Chapter 3. There were slight experimental differences: in Chapter 3, we implemented individually-adjusted cardio-audio delays, whereas in Chapter 2, we presented fixed delays. This is inconsistent with precision-weighted predictive coding frameworks and previous research, which demonstrate attention as a mechanism of precision optimisation (Ainley et al., 2016; Chennu et al., 2013, 2016; Critchley et al., 2004; García-Cordero et al., 2017; Garrido et al., 2009; Hohwy, 2012; Montoya et al., 1993; Petzschner et al., 2017; Raij et al., 1997; Schandry et al., 1986; Villena-González et al., 2017; Yuan et al., 2007). However, it is possible that tailoring the cardio-audio delays to each individual enhanced the perception of cardio-audio synchrony in more participants. Hence, there was less reliance on attention to boost predictive mechanisms. Therefore, when employing a more refined paradigm with enhanced perceived synchrony, as demonstrated in the trend of improved performance, results may more accurately represent interoceptive-exteroceptive integrated mechanisms (i.e., not dependent on attentional modulation). Although in Chapter 3, we didn't observe a post-omission attention and delay interaction, we did observe an omission-locked main effect of delay, which overlaps in time with the interaction effect in Chapter 2. Thus, cardio-audio predictive mechanisms were present but not modulated by attention. This is consistent with Pfieffer & De Lucia's et al (2017) findings of cardio-audio 'prediction error', as this effect was observed while participants passively listened to sounds (i.e., without direct attention). Thus, when accounting for individual differences in perceived synchrony in Chapter 3, we fail to support the necessity of attention for forming integrated cardio-audio predictive mechanisms (as evidenced in Chapter 3 by strong Bayesian evidence for the null hypothesis).

5.3.3 Trait Precision Modulation

Similar to the role of attention as a state measure of precision within individuals, an enhanced ability to perceive internal sensations is thought to modulate predictive mechanisms as a measure of trait precision between individuals. For example, those with high interoceptive abilities are proposed to prioritise interoception over other sensory modalities by enhancing the relative precision of interoceptive prediction and prediction error signals, resulting in more accurate interoceptive models over time (Ainley et al., 2016). We hypothesised that those with high heartbeat perception are able to enhance the relative precision of interoceptive prediction and prediction error signals over other modalities, and therefore will modulate integrated cardio-audio predictive mechanisms. Thus, we measured interoceptive ability (sensitivity, accuracy, and awareness) to investigate the influence of trait precision on integrated cross-modal predictive mechanisms.

In Chapters 2 and 3, we failed to observe evidence of trait precision modulation of predictive mechanisms by objective, subjective and metacognitive interoceptive ability dimensions. This is inconsistent with precision-weighted predictive coding accounts, in which individual differences in interoceptive perception should modulate the precision of predictive mechanisms. This is further incompatible with previous research, which demonstrate interoceptive accuracy modulates the HEP response (Katkin et al., 1991; Pollatos et al., 2005; Pollatos & Schandry, 2004; Schandry et al., 1986). However, those studies measured interoceptive ability using a heartbeat counting task, contrary to the heartbeat discrimination task employed in our experiments. Indeed, the measurement of interoceptive performance is challenging because it is impossible to manipulate interoceptive stimuli, unlike exteroceptive detection tasks (i.e., vision, audition, somatosensory) (Al et al., 2020; Salkoff et al., 2020; Wright & Fitzgerald, 2004). Furthermore, the two most dominant methods of measuring interoceptive performance: heartbeat tracking and heartbeat discrimination tasks, both have significant flaws. For example, the heartbeat discrimination task (in Chapter 2) is based on assumptions about when individuals feel their heartbeat during the cardiac cycle. Generally, a shorter delay from the ECG R-peak, closer to ventricular contraction (i.e., systole), is assumed to be when heartbeat sensations are perceived. While a longer delay, presumed to be during cardiac relaxation (i.e., diastole), is considered to be a period of reduced heartbeat sensations (otherwise known as signal plus and signal minus). However, research using the Method of Constant Stimuli in which sounds are presented at six delays from the heartbeat reveals large individual differences in the preferred interval. Therefore, there is high variability in the perceived timing of heartbeat sensations (Brener et al., 1993a; Brener & Ring, 2016). Consequently, we postulated the lack of interoceptive ability effects in Chapter 2 might result from individual differences in the perceived timing of heartbeat sensations. Thus, in Chapter 3, we individually tailored the cardio-audio delays to more accurately measure interoceptive performance, and therefore, trait precisional influences on predictive mechanisms.

Although we improved the two-interval heartbeat discrimination task by determining the individual preferred interval of heartbeat perception (Brener & Kluvitse, 1988; Mesas & Chica, 2003), interoceptive performance did not significantly improve. Furthermore, there remain difficulties with the task. For example, all heartbeat discrimination tasks rely on multisensory integrative ability of determining the synchronicity of interoceptive and exteroceptive input. Although this mechanism is essential for embodied selfhood, this task is cognitively challenging and an indirect method of assessing interoceptive ability. Consequently, these difficulties may impede the accuracy of detecting interoceptive performance. Thus, the lack of observed modulation of predictive mechanisms by interoceptive ability may be a result of measurement challenges. An alternative task that many studies employ is the heartbeat counting task, a direct measure of heartbeat performance that involves counting or tapping the number of heartbeats during specific intervals. Despite being widely used, it has numerous confounds. One of the major concerns of these tasks is that participants can guess the general rhythm, and therefore, the count of their heartbeats. For example, those with more experience or knowledge of the general rhythm of their cardiac cycle (i.e., athletes and medical professionals) have falsely enhanced scores. This was confirmed when the counting score of these experienced professions was reduced when asked explicitly to count only felt heartbeats and not estimated heartbeats (Desmedt et al., 2018, 2020; Murphy et al., 2018). Furthermore, other studies found that individuals' prior beliefs of their heart rate are more predictive of heartbeat counting scores than their actual heartbeat. Moreover, these scores are primarily influenced by lower estimates of the heart rate (Ring & Brener, 1996; Zamariola et al., 2018). Therefore, heartrate beliefs highly influence heartbeat counting scores, and consequently, heartbeat counting performance should be interpreted with caution.

Future research could investigate a recent heart rate discrimination task that may more accurately assess interoceptive ability (Legrand et al., 2021). This task asks participants to report whether a series of tones are faster or slower than their perceived heart rate. Furthermore, a matched exteroceptive task is implemented to control for working memory and time estimating ability. Psychometric and metacognitive curves are generated by investigating beliefs regarding changes in heart rate based on a Bayesian psychophysical approach. This approach includes measurements of accuracy, bias, and precision of interoceptive beliefs. Therefore, this task could be investigated with our paradigm in future research.

Our design's short successive auditory stimuli prevented the investigation of late latencies associated with high-level metacognitive effects (i.e., between 550-1900ms) (Skavhaug et al., 2010; Sommer et al., 1995; Tsalas et al., 2018). Hence, trait precision (via interceptive performance) may operate at later latencies than could be observed in our paradigm. Moreover, long-range connectivity patterns of global activity have been associated with interoceptive metacognitive awareness during a heartbeat tapping task, instead of differences in HEP local activity (Canales-Johnson et al., 2015). Therefore, future research could investigate these connectivity markers during our paradigm to reveal the influences of trait precision on interoceptive-exteroceptive integration.

5.3.4 Consciousness

Embodied cognition frameworks portray the interaction of internal bodily signals with the brain as imperative for cognition and consciousness (Craig, 2009; A. Damasio, 2010; Seth, 2013; Seth & Friston, 2016). In particular, neural representations of the body are fundamental for minimal pre-reflexive aspects of selfhood, such as the sense of 'mineness' or ownership of experience. For example, perceiving, moving, or thinking is accompanied by a pre-reflexive sense that these experiences, movements, and thoughts belong to (i.e., ownership) and are caused by (i.e., sense of agency) ourselves (Gallagher, 2010; Gallagher & Zahavi, 2012). Thus, embodied pre-reflexive self-awareness is interwoven with conscious experience, suggesting its neural signatures may provide valuable information regarding the recovery of consciousness after severe brain injury. As described in the 'Research Questions and Rationale' section, numerous studies have demonstrated the role of internal cardiac signals for broad facets of selfhood, such as body-ownership, self-location, and self-identification (Aspell et al., 2013; Heydrich et al., 2018; Sel et al., 2017; Suzuki et al., 2013; Tajadura-Jiménez et al., 2012; Tsakiris et al., 2011). Furthermore, neural signatures of cardiac processing (i.e., heart-evoked potentials) fluctuate with self-cognitive dimensions (Babo-Rebelo et al., 2016, 2019; Park et al., 2014; 2017). Hence, the heart-evoked potential may provide an ideal marker of embodied pre-reflexive self-awareness in acute unresponsive patients, as the neural signature is independent of behavioural response and represents a core embodied self-awareness component of subjective experience.

By definition, a patient with a disorder of consciousness (including those acutely unresponsive) lacks awareness of their self and their environment (Royal College of Physicians, 2020). Despite the dual diagnostic criteria, current consciousness diagnostic tests focus solely on assessing responses to external stimuli in the environment, leaving self-awareness unexplored (Royal College of Physicians, 2020; Schnakers, 2012). Accurate prognostication and diagnosis of consciousness is crucial for critical care decisions such as life-sustaining treatment decisions and rehabilitation assignments (Kitzinger & Kitzinger, 2018). Thus, characterising all aspects of awareness (of self and environment) is fundamental for improving diagnostic and prognostic accuracy. Accordingly, Chapter 4 investigated the prognostic potential of resting heart-evoked potentials (i.e., a neural signature of embodied self-awareness) to predict recovery from acute unresponsive states (Babo-Rebelo et al., 2016, 2019; Park et al., 2014; 2017).

We did not observe evidence of the predictive utility of HEPs for the recovery of awareness from acute unresponsiveness, aside from a single time-point (211ms post-R) which significantly predicted outcome at six months. Because this effect is only present at a single time point, this effect is likely due to chance. Furthermore, the result does not persist without CFA correction, suggesting the CFA correction method induced artefactual differences. Methods of CFA correction (i.e., such as ICA) can reduce the CFA, however, it is impossible to determine if the CFA is eradicated completely (Azzalini et al., 2019). Thus, if the CFA is differentially removed in certain conditions/individuals than others, comparisons can insert artefactual CFA differences. This demonstrates the importance of control analyses which ensure heartbeat-locked effects persist with and without CFA correction. In our case, the single time-point HEP effect predictive of 6-month outcome is only present with CFA correction, not without. Hence, it is likely this effect is a result of chance or CFA correction artefacts.

Our lack of significant prognostic effects of resting HEPs in acute unresponsive patients is inconsistent with previous research, which highlights the diagnostic value of HEPs in chronic disorder of consciousness patients (Candia-Rivera et al., 2021; Raimondo et al., 2017). HEPs may contain information related to consciousness at the time it is present but do not prospectively predict the recovery of consciousness. For example, HEPs may reflect interoceptive mechanisms which contribute towards self-reflexive awareness when conscious, but these mechanisms are substantially reduced or absent when unconscious. Indeed, HEP amplitude reduces with sleep depth but increases during REM sleep and wakefulness (Lechinger et al., 2015; Simor et al., 2021). However, it is difficult to ascertain the state of consciousness of our patients at the time of EEG recording. We assessed acutely unresponsive patients after the complete wash-out of sedation. Therefore, it is possible that some patients were covertly aware at this point but behaviourally unresponsive or alternatively unaware in an early vegetative state. If covert awareness were present, we would expect those with self-awareness at the time of EEG recording to have a better outcome at three or six months and for this to be reflected in their HEPs. However, we found no indication of this. A more in-depth assessment of the consciousness state of patients at the time of EEG would assist with determining whether patients need to be conscious for HEPs to be clinically valuable. For example, the Coma Recovery Scale provides a more fine-tuned assessment of consciousness than the Glasgow Coma Scale used in our study (Giacino et al., 2004). However, behavioural scales do not account for patients who cannot behaviourally respond but have covert cognitive abilities. Thus, comparing neural signatures of conscious cognition such as those reflecting high-level language comprehension may be more beneficial for future research (Gui et al., 2020; Rohaut et al., 2015; Sokoliuk et al., 2019).

The inclusion criteria of our study were specifically centred towards measuring an important subset of patients most in need of an improvement in prognostic accuracy – those who do not obey commands after sedation has washed out. Although this is an important subset of patients, our inclusion requirements resulted in a reasonably small final sample, with low variation in consciousness outcome (i.e., only three patients were unconscious or dead, while 14 recovered consciousness, each at three and six months,). A larger sample with higher variation in consciousness outcome may reveal alternative prognostic HEP effects. A further limitation is our outcome assessments were completed over the phone with a next of kin rather than an extensive in-person assessment by a trained clinician. These outcome assessments were primarily focused on behavioural recovery. Thus, future research could complete a more in-depth evaluation of the patients' recovery of cognitive capabilities, especially those relating to interoceptive processing such as selfhood and emotional processing. This may reveal more informative prognostic effects of the HEP. Indeed, previous research demonstrated the diagnostic value of HEPs for distinguishing between consciousness state diagnoses (Candia-Rivera et al., 2021; Raimondo et al., 2017). However, Raimondo et al (2017) did not apply CFA correction to HEP responses. Thus, the HEP differences in that study may be driven by low-level cardiac activity rather than neural HEP effects. Nonetheless, Candia-Rivera et al (2021) revealed CFA-corrected HEP responses differentiated between VS/UWS and MCS patients with high accuracy. Interestingly, they had disproportionate diagnoses of consciousness state (7 VS/UWS vs 31 MCS), similar to our low variability in consciousness outcomes. However, they implemented a machine learning approach, which is potentially problematic with unbalanced consciousness diagnoses as this may bias classification accuracy. Therefore, more research is needed with a larger balanced sample to reveal the value of HEPs for consciousness diagnoses and prognoses.

Finally, we included HEPs during rest, whereas investigating HEPs during a higher-level task that actively engages self-processing may be informative. Potential self-cognitive paradigms include those that previously were successful at modulating HEP amplitude. For example, patients could be asked to complete an imagination task that involves shifting their imagined perspective from first-person to third-person and vice-versa (Babo-Rebelo et al., 2016, 2019). Subsequently, those with HEP modulations that varied with imagined perspective would demonstrate preserved self-cognitive capabilities, and thus, predict recovery of overt responses associated with these abilities. However, the high cognitive demands of this task may be too challenging for those with severe brain injury. Therefore, passive HEP self-cognitive tasks may be more appropriate, such as presenting self-related vs other-related words (i.e., first vs third person tense or the patient's name/voice). Indeed, 25% of patients with a disorder of consciousness demonstrate different ERP responses to their own name, in comparison to an other's name (Kempny et al., 2018). Comparing these name/other responses during HEPs may elicit internal self-processing more directly, potentially enhancing the detection of this response in more patients.

Alternatively, future research could observe evidence of interoceptive-exteroceptive integration, indicating the preservation of pathways necessary for a first-person perspective and pre-reflexive forms of selfhood (Allen et al., 2020; Limanowski & Blankenburg, 2013; Marshall et al., 2018; Seth & Friston, 2016; Tallon-Baudry et al., 2018). For example, our novel paradigm implemented in Chapters 2-3 provides an ideal method for investigating interoceptive-exteroceptive integrative capabilities (Banellis & Cruse, 2020, 2021). Indeed, we observed robust HEP evidence of heartbeat-driven expectations of sounds. This signature of interoceptive-exteroceptive integration was observed by comparing trials with sounds at different delays from the heartbeat. Observing this HEP effect in acute unresponsive patients may demonstrate the ability to integrate information within and outside the body, thus predicting the recovery of associated self-aware processes. Importantly, this cardio-audio expectation effect was independent of individual ability to perceive heartbeat sensations. Therefore, this HEP effect can be observed in all patients with various interoceptive perception abilities. Furthermore, this effect was not dependent on attention to internal sensations, and thus, can be presented passively to patients. Passive presentation is especially ideal for those with reduced cognitive capabilities due to severe brain injury. In contrary, previous prognostic research with pre-attentive cognitive markers such as the MMN and P3 response predicted only the recovery of wakefulness rather than awareness. Thus, a higher-level omission HEP response may be necessary to predict awareness recovery. For example, this could involve presenting emotional or self-related words/sounds at different delays from the heartbeat instead of the meaningless tones in our paradigm.

5.4 Limitations of HEPs

Researching neural responses locked to bodily signals is complicated by ongoing bodily electrophysiological responses. For example, electrical activity from the heart can contaminate neural electroencephalography recordings. Therefore, when analysing neural responses locked to the heartbeat (i.e., heart-evoked potentials), it is essential to control for the cardiac field artefact. This is especially important when comparing neural responses during different phases of the cardiac cycle (i.e., as in our post-omission analyses), as the increased cardiac activity during systole (ventricular contraction), relative to diastole (rest), could insert artefactual effects. Thus, it was vital we controlled for the CFA sufficiently. CFA correction options include ICA, rest/nose template subtraction, Hjorth source derivation, current source density transformation, or restricting analyses to a time window of minimal CFA-influences (typically R-peak+455-595ms). In Chapter 3, we compared two of these CFA correction methods: rest template subtraction and ICA correction, to determine which best attenuated the CFA (see Supplementary Figure 18). ICA reduced the CFA more than a rest template subtraction, calculated by the ratio of the sum of the root mean square of channels across time of corrected HEP data with that of non-corrected HEP data. Hence, we employed ICA as the CFA correction method in Chapters 3-4, which is also is the most common correction method (Coll et al., 2021b). Despite observing evidence of ICA substantially reducing the CFA, there remains several problems with CFA correction. For example, it is impossible to determine if the CFA has been attenuated completed or if some of the HEP effect of interest has been removed as a consequence. Furthermore, the CFA correction method can insert artefactual differences if the CFA is diminished more in one condition/group than another. Thus, a control analysis without CFA correction is necessary to ensure results are not a consequence of artefacts inserted from the method. Because of these issues, additional control analyses on cardiac activity (i.e., ECG, heart rate, and heart rate variability) are useful for ensuring differences in cardiac activity between conditions/groups do not exist. Therefore, these cardiac control analyses provide additional reassurance that differences in cardiac activity do not contribute towards HEP results.

In addition to the variability in CFA correction methods and control analyses, other HEP preprocessing procedures also lack standardisation. For example, there is disagreement regarding whether baseline correction should be applied to HEP responses, and if so, which baseline window should be selected. Some studies implement a baseline correction window of -100ms/-200ms to 0ms, which is standard for many ERP studies (Judah et al., 2018; Mai et al., 2018; Marshall et al., 2018). However, the QRS complex of the ECG can insert artificial differences in HEPs. Thus some apply a baseline window that avoids the QRS complex (i.e., -150ms to -50ms) (Schandry et al., 1986; Sel et al., 2017). Along with previous studies (Azzalini et al., 2019; Babo-Rebelo et al., 2016, 2019; Park et al., 2014b; Petzschner et al., 2019), we applied no baseline correction. This is because cardiac activity is cyclical by nature, thus, there is no baseline period free of cardiac processing. For example, the period before HEP onset includes cortical processing of the previous heartbeat or potentially preparatory commands for the present heartbeat (Azzalini et al., 2019). Therefore, applying baseline correction of any window may insert artefactual effects. Nevertheless, no baseline correction risks the influence of ‘baseline’/pre-heartbeat differences driving HEP effects. In fact, we were concerned of baseline differences for the post-omission main effect of delay effect in Chapter 3. Consequently, we performed control analyses with and without baseline correction to ensure our HEP effects were not due to baseline differences or analytical confounds (see Supplementary Figure 19 and Supplementary Table 7). Furthermore, the window of baseline correction (or lack of) influences the polarity of results, therefore polarity differences across conditions without baseline correction should be interpreted with caution.

Furthermore, HEPs have multiple potential interpretations. For example, some interpret HEPs to reflect interoceptive predictive mechanisms, with the amplitude proposed to reflect precision-weighted prediction error regarding each heartbeat (Ainley et al., 2016). The predictive interpretation of HEPs have been discussed in more detail above (see 'cardio-audio expectation', 'state-precisions modulation' and 'trait-precision modulation' sections above). Alternatively, HEP amplitude may reflect sensory processing of cardiac activity. This is supported by research demonstrating the modulation of HEP amplitude by interoceptive accuracy (i.e., heartbeat sensation) (Katkin et al., 1991; Pollatos et al., 2005; Pollatos & Schandry, 2004; Schandry et al., 1986). Moreover, HEPs have been observed to fluctuate with broad cognitive processes, including emotion and self-processing (Couto et al., 2015, Park et al., 2018, Sel et al., 2016). Therefore, HEP amplitude may not be limited to sensory interpretations but also higher-level cognitive processes.

5.5 Future Directions

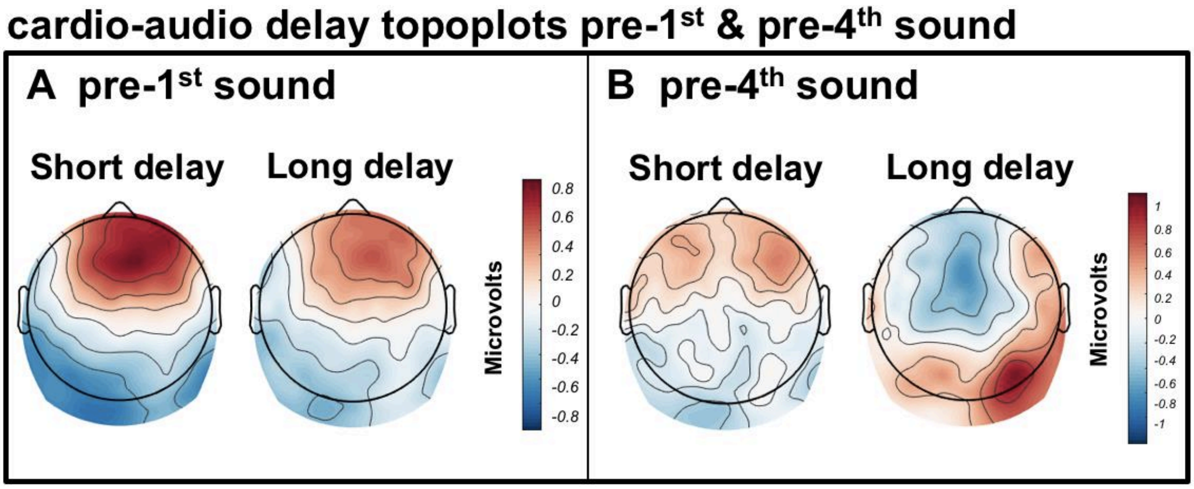
We found evidence of integrated interoceptive-exteroceptive predictive mechanisms in HEPs. These mechanisms are proposed to be important for embodied self-consciousness and emotional subjective experiences. Therefore, future research could test whether our signature of interoceptive-exteroceptive integration fluctuates with self-processing or emotional experience. This could be investigated by integrating a cognitive element into the cardio-audio paradigm. For example, as suggested in the 'Consciousness' section: emotional or self-related words/sounds could replace the basic tones previously implemented in Chapters 2-3. This could include auditory stimuli which elicit or describe certain emotions (i.e., fearful screams or pleasant musical tones) or initiate self-cognitive processes (i.e., hearing their name or voice). This would reveal if emotion or self-cognition modulates interoceptive-exteroceptive integration, supporting the involvement of these integrated mechanisms in high-level processes. Additionally, healthy integrated cross-modal HEP responses could be compared with patients with clinical conditions of disturbed selfhood (i.e., depersonalisation disorder or schizophrenia) or emotional processing (i.e., alexithymia). Furthermore, the development of interoceptive-exteroceptive integrated processes could be investigated in infants of different ages. Indeed, the detection of cognitive capabilities in infants face similar challenges to unresponsive patients as they both cannot report on their experiences coherently. Thus, implementing our cross-modal task in infants may indicate their capacity for interoceptive-exteroceptive integration and related self-cognitive processes. Finally, presenting our paradigm passively without a task or while asleep/sedated would determine the extent these cross-modal mechanisms depend on consciousness and reveal its suitability for application in DOC patients. Another interesting avenue for future research could involve perturbatory methods such as vagus nerve stimulation (VNS) (Paciorek & Skora, 2020; Richter et al., 2021; Villani et al., 2019; Weng et al., 2021). This can be implemented non-invasively via transcutaneous auricular placement, ideal for DOC patients. For example, observing healthy EEG responses to VNS such as theta and delta increases in frontal regions would demonstrate the integrity of interoceptive pathways. Hence, VNS is potentially valuable for prognoses of self-awareness in DOC patients (Machetanz et al., 2021).

5.6 Summary & Conclusions

In summary, we observed robust evidence of heartbeat-driven expectations of sounds reflected in HEPs during an integrated heartbeat detection and omission detection task. This suggests interoceptive-exteroceptive integration functions predictively, as described by predictive coding frameworks. However, we observed inconsistent evidence of the modulation of these integrated predictive mechanisms by attentional/state precision. Furthermore, we observed no evidence of the influence of individual differences in interoceptive performance (i.e., trait precision). Thus, our findings are not compatible with precision weighting properties of predicting coding accounts. However, difficulties in evaluating interoceptive performance may impede the accurate assessment of trait precision influences. Moreover, future research may employ stronger manipulations of state precision, such as comparing integrated HEP responses during sleep and wakefulness. This may reveal the suitability of these integrated interoceptive-exteroceptive HEP responses for assessing consciousness state in DOC patients. Finally, we observed no evidence of the prognostic utility of resting HEP responses or cardiac measures in predicting recovery from acute unresponsiveness. However, future research is needed with a larger sample and greater variability in outcome, as well as more thorough consciousness assessments at the time of HEP recording. Investigating HEP responses during tasks that engage interoceptive-exteroceptive integrative mechanisms or high-level emotional or self-cognitive processes may provide greater prognostic value of the recovery of awareness, as well as perturbatory methods such as vagus nerve stimulation.

SUPPLEMENTARY MATERIAL A (FOR CHAPTER 2)

6.1 Control pre-first and pre-fourth delay comparisons



Supplementary Figure 17. *Topoplots of the average activity 27ms-230ms relative to the R-peak before the first sound and before the forth sound for each cardio-audio delay condition.*

SUPPLEMENTARY MATERIAL B (FOR CHAPTER 3)

6.1 ERP analysis details

Supplementary Table 5. *Details of ERP analyses.*

Comparison	Time window	Tail
1. Perceived synchronous AEPs (most rated synchronous) and perceived asynchronous AEPs (least rated synchronous) during part 1.	First three auditory components determined by GFP and GMD: 0-74ms, 74-154ms, 154-209ms. Exploratory analysis of fourth and fifth auditory component: 209-289ms, 289-500ms.	Two-tailed.
2. Perceived synchronous HEPs (most rated synchronous) and perceived asynchronous HEPs (least rated synchronous) during silent periods at the end of part 1 trials.	Separate time windows for the perceived synchronous cardio-audio delay (highest simultaneous judgement) and the perceived asynchronous cardio-audio delay (lowest simultaneous judgement) + 250ms each. For example, if the perceived synchronous delay was 213ms and the asynchronous delay was 510ms, the time windows would be 213-463ms and 510-760ms. Also, R-peak to earliest perceived synchronous cardio-audio delay (113ms).	Two-tailed. Two-tailed.
3. Comparison 1 and 2 in high and low heartbeat perceivers separately (exploratory).	As comparison 1 and 2.	As comparison 1 and 2.
4. Cardio-audio delay (perceived synchrony) and attention.	R-peak to earliest perceived synchronous cardio-audio delay (129ms: defined as the 1st percentile of the R->Sound intervals of p14	Two-tailed

5. Interoceptive ability and cardio-audio delay, during internal trials.	(participant with the lowest perceived synchronous delay). Banellis and Cruse (2020) attention and cardio-audio delay interaction time window (95ms-138ms relative to the omission)	One-tailed (perceived synchronous more positive)
6. Interoceptive ability and attention, during synchronous trials.	R-peak to earliest perceived synchronous cardio-audio delay (129ms: defined as the 1st percentile of the R->Sound intervals of p14 (participant with the lowest perceived synchronous delay).	Two-tailed
	Banellis and Cruse (2020) attention and cardio-audio delay interaction time window (95ms-138ms relative to the omission)	Two-tailed

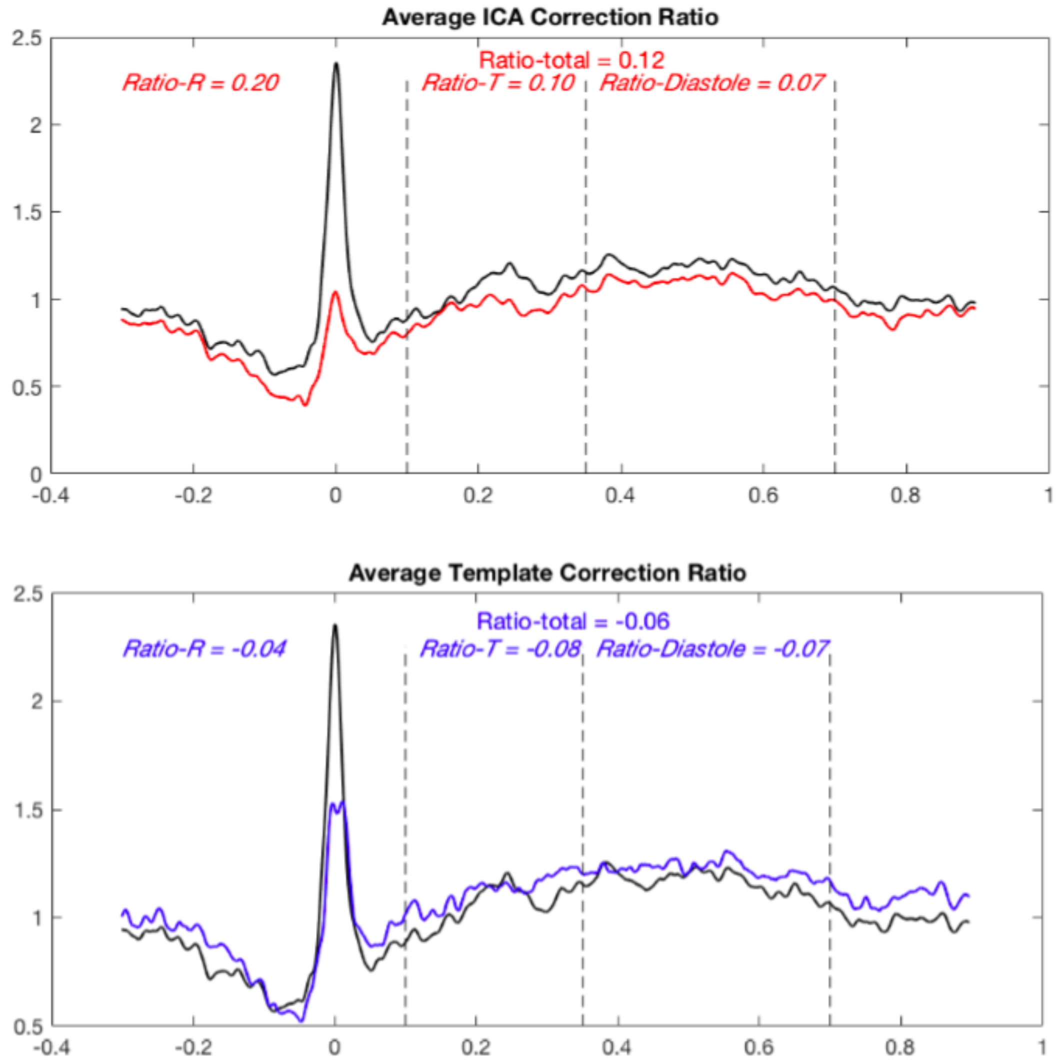
6.2 Individual performance

Supplementary Table 6. *Individual performance. 'Med' is the median (perceived synchronous) interval calculated from the linearly interpolated cumulative distribution of choices from the MCS task. 'Max Int' and 'Min Int' are the maximum and minimum delays rated as synchronous with the heartbeat during the MCS. 'IQR' is the difference between the 75th and 25th quartile of the linearly interpolated cumulative distribution of choices from the MCS task. To account for the computational lag when triggering a sound from the online detection of R-peaks, we added 113ms (i.e. average cardio-audio computational lag) to the Med and IQR columns, which were calculated from values inputted into the computer for the experiment. 'Chi2' on MCS simultaneous ratings: if significant ('sig') participants were classified as a high heartbeat perceiver, if not significant ('not sig') participants were defined as a low perceiver. 'Internal d'' (i.e. interoceptive accuracy) reflects d-prime of internal task performance. 'External d'' (i.e. exteroceptive accuracy) is the d-prime of external task performance. 'BPQBA' is the score on the Porges body perception questionnaire (short form) body awareness subsection, and 'BPQANS' is the score on the autonomic nervous system reactivity subsection (i.e. both reflect interoceptive sensibility to all body sensations). 'Heart Conf' is the median confidence rating during the internal task (i.e. interoceptive sensibility to heart sensations specifically). 'Tone Conf' is the median confidence ratings during the external task. 'M_diff' is meta d-prime, calculated as the difference between type 2 sensitivity (meta-d') and expected type 2 sensitivity (d') (i.e. meta-d' – d'; interoceptive metacognitive awareness).*

ID	Med	Max Int	Min Int	IQR	Chi2	Internal d'	External d'	BPQBA	BPQANS	Heart Conf	Tone Conf	M_diff
p04	309	612	510	423	not sig	0.589	2.848	69	37	2	4	-0.666
p05	248	213	612	362	sig	0.932	4.200	69	27	3	4	-0.979
p06	318	213	314	428	not sig	0.740	3.446	54	25	3	4	-1.239
p07	281	314	612	345	sig	0.000	2.590	47	24	2	3	-0.087
p08	299	213	612	399	not sig	-0.123	1.334	98	36	3	3	0.653
p09	301	113	314	428	not sig	0.131	3.118	83	39	2	3	-0.246
p11	325	213	113	432	sig	0.546	3.951	61	24	2	4	-0.921
p12	294	213	413	428	not sig	0.190	2.774	89	38	2	4	-0.735
p13	331	612	113	410	not sig	-0.275	4.482	80	37	2	4	0.070
p14	158	113	510	275	sig	2.166	2.433	69	39	4	4	-0.903
p15	294	113	314	469	not sig	0.272	1.570	30	23	2	3	0.181
p17	329	113	314	454	not sig	0.019	3.425	53	33	2	4	0.278
p18	354	510	213	415	not sig	-0.184	1.589	84	35	3	3	0.175
p19	301	113	612	422	not sig	0.672	2.724	67	28	2	3	-0.557
p20	309	213	612	385	not sig	0.456	2.517	94	31	3	3	-1.210
p21	271	314	510	344	sig	0.607	3.337	87	35	3	4	-0.366
p22	358	510	113	416	not sig	0.502	1.358	79	42	4	4	-0.260
p23	314	612	314	422	not sig	1.080	3.016	108	45	4	4	-1.351
p24	300	113	314	432	not sig	-0.019	3.325	52	42	4	4	0.078
p25	293	213	413	427	not sig	0.317	2.948	112	27	3	3	-0.477
p26	293	213	510	414	not sig	-0.012	4.520	57	25	3	4	0.020
p27	304	113	510	426	not sig	0.241	3.725	73	30	2	3	-0.655
p28	272	113	413	464	sig	-0.191	3.134	45	21	3	4	-0.125
p29	314	213	314	425	not sig	0.047	1.694	122	23	2	2	-0.434
p30	296	113	510	405	not sig	0.453	4.241	74	47	3	4	0.115
p31	317	413	213	401	not sig	0.146	1.365	34	23	3	3	-0.299
p32	208	213	510	301	sig	1.581	4.256	53	25	2	4	-0.210
p33	304	314	413	421	not sig	0.205	4.483	42	22	1	4	-0.144
p34	253	113	413	444	sig	0.423	4.241	51	26	2	4	-0.326
p35	302	213	413	409	not sig	-0.445	3.134	49	31	4	4	0.115
p36	347	510	314	412	not sig	0.594	4.520	60	22	2	4	-1.018
p37	257	213	510	389	not sig	0.200	2.932	88	33	3	4	0.237
p38	314	612	413	454	not sig	0.536	4.200	88	26	1	4	-0.757
p39	326	213	113	411	not sig	0.271	2.247	125	23	3	4	-0.790
p40	255	113	612	381	sig	0.140	3.929	98	37	2	4	-0.373

6.3 CFA correction method

Compared CFA correction methods (ICA vs rest template subtraction), using a previously pre-processed form of the dataset in this paper, with -100ms to 0ms baseline correction (in accordance with the previous preregistered pre-processing pipeline). Time windows for each cardiac event was defined as follows: R period -100ms to 100ms, T period -100 to 350ms, Diastole period 350ms to 700ms, and the total window -100 to 900ms. The ratio was calculated as the division of the sum of the root mean square across channels per time point for the CFA corrected average, by the sum of the root mean square across channels per time point for the raw data average, minus 1 ($Ratio\ ICA = 1 - \frac{\sum_{time}(rms_{channel}(clean\ data))}{\sum_{time}(rms_{channel}(raw\ data))}$). Therefore, a higher number represents greater reduction of the CFA.



Supplementary Figure 18. *Black line in both figures reflects averaged HEP response before CFA correction. Red line in the top figure reflects averaged HEP response after ICA CFA correction, and* *blue line in bottom figure reflects averaged HEP response after rest template CFA subtraction. Ratios calculated as stated above the figure.*

6.4 Control Analyses

6.4.1 HEP Control Analyses

To ensure the R-locked main effect of delay is task-dependent and not a result of residual HEP differences, we analysed the difference between delay conditions before the first and fourth sound. We chose the fourth sound as the omission could occur from the fifth sound onward. Therefore, we computed robust averages of pre-processed HEP data relative to the R-peak for the first and fourth sound. We averaged pre-sound HEP activity belonging to the electrodes and time-window of the significant pre-omission positive cluster, for each participant. Subsequently, a two-way ANOVA analysed the interaction of cardio-audio delay (short and long delay) and sound number (first and fourth sound) and t-tests analysed the effect of cardio-audio delay separately for the first and fourth sound.

6.4.2 Baseline and CFA correction controls

To test whether the omission-locked delay effect was driven by pre-omission baseline differences (see Figure 14), we performed the same comparison using the time of the significant effect (compared delay conditions 94-137ms post-omission), with two baseline correction windows (-100ms to 0ms (Pfeiffer and De Lucia., 2017; Marshall et al., 2017; 2018) and -150ms to -50ms (Sel et al., 2018; Canales-Johnson et al., 2015)). Additionally, to ensure our CFA correction method did not insert artificial effects by removing cardiac artefacts more in one condition than the other, we additionally analysed the data without CFA correction. This resulted in five control comparison combinations (-100ms to 0ms baseline correction with CFA correction, -150ms to -50ms baseline correction with CFA correction, -100ms to 0ms baseline correction with no CFA correction, -150ms to -50ms baseline correction with no CFA correction, no baseline correction with no CFA correction), in addition to the standard no baseline correction with CFA correction analyses reported throughout the paper. Equally, we completed the same five control comparisons to all ERP results which demonstrated a significant sensor level effect.

6.4.3 CFA Control Analyses

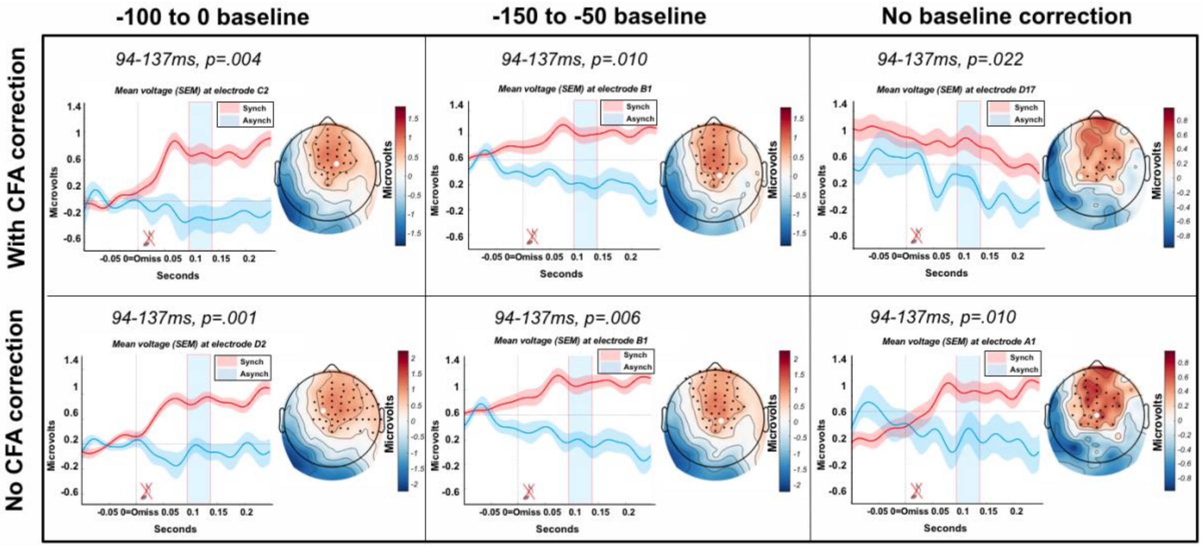
We performed control analyses on the ECG data, to determine if differences in cardiac activity contributed towards the HEP results. Therefore, we completed equivalent analyses to that which demonstrated significant ERP results on the ECG data. Subsequently, we computed single-subject robust averages of the ECG activity for each condition and analysed them using the cluster mass method, as described above. We completed ECG comparisons as to those which showed a significant ERP effect (i.e. for part 1 we compared ECG across perceived synchrony conditions time-locked to sounds 176-209ms and 240-289ms in high perceivers only. For part 2 we compared cardio-audio delay conditions 79-128ms post-R and 94-137ms post-omission, compared attention conditions 37-68ms post-R, assessed the attention and interoceptive awareness interaction 96-139ms post-omission, and assessed the pairwise effect of attention during synchronous trials in high awareness participants 105-131ms post-omission).

6.4.4 Control HEP results

We would expect a true cardio-audio expectation effect to be present not only pre-omission but also pre-sound, perhaps increasing in strength as expectation builds with the number of R-locked sounds. To test this, we analysed the main effect of delay before the fourth sound and compared this to the pre-first sound delay effect (before any sounds), using the electrodes and time window of the significant positive pre-omission cluster (R+79-128ms). Although this revealed a not significant sound number and delay interaction ($F(1,33) = 0.898$, $p = .350$, $n^2 = 0.007$, $BF_{incl} = 1.524$), there was a greater delay effect before the fourth sound (Mean delay difference = 0.322), in comparison to before the first sound (Mean delay difference = 0.175).

6.4.5 Baseline and CFA correction control results

All baseline correction and CFA correction control combinations (-100 to 0, -150 to -50 and no baseline correction and with/without CFA correction) demonstrated a significant main effect of cardio-audio delay relative to the omission (largest $p = .022$), therefore CFA correction and baseline effects did not influence the omission-locked delay effect (see Supplementary Figure 19).



Supplementary Figure 19. The omission-locked delay effect with and without baseline correction (-100 to 0 and -150 to -50), as well as with and without CFA correction.

The R-locked main effect of delay was significant in all control comparisons (largest *p* = .024), although four of the control comparisons demonstrated positive and negative significant clusters rather than a sole positive cluster as demonstrated in our primary analysis results, suggesting this effect may involve broader neural regions. The R-locked main effect of attention and omission-locked attention and interoceptive awareness interaction was present in two out of the five control comparisons, with marginal significance in an additional control comparison each, suggesting that these may reflect weak effects. The 176-209ms AEP result in high perceivers was present in three and the 240-289ms AEP result was present in four out of the five control comparisons, with marginal significance in an additional control comparison for each time window (see Supplementary Table 7).

6.4.6 Control ECG results

We observed no significant differences in ECG responses between cardio-audio delay conditions 79-128ms post-R (no clusters) or 94-137ms post-omission (*p* = .128), or between attention conditions 37-68ms post-R (no clusters). Additionally, we observed no ECG differences between most rated synchronous AEPs and least rated synchronous AEPs in high perceivers, 176-209ms and 240-289ms relative to the sound (no clusters). Additionally, no significant ECG interaction of attention and awareness 96-139ms and no significant ECG simple effect of attention in high aware participants 105-131ms, post-omission and during synchronous trials only (no clusters). Therefore, it is unlikely that ECG activity contributed towards the ERP differences observed.

6.5 Interbeat intervals (IBI's)

We analysed the IBI's throughout experimental blocks (after the removal of faulty blocks with IBI's smaller than 400ms or larger than 1500ms). Replicating our previous study, we found that IBI's were significantly longer when internally attending (M=838.413, SD=82.548) than when attending externally (M=827.287, SD=83.351; F(1,33) = 22.072, *p* <.001, n^2 = 0.274, BF_{incl} = 430383.021). There was no significant IBI difference across delay conditions (F(1,33) = 0.017, *p* = .896, n^2 = 1.026e-4, BF_{incl} = 0.157), and no significant interaction of delay and attention (F(1,33) = 0.854, *p* = .362, n^2 = 0.003, BF_{incl} = 0.180). Thus, we can conclude that overall heart-rate differences did not influence our HEP delay effects.

Additionally, as previous studies found heart rate differences in response to omission and deviant stimuli (Banellis & Cruse, 2020; Pfeiffer & De Lucia, 2017; Raimondo et al., 2017), we investigated differences surrounding the within-task omissions. Thus, we compared the IBI around the omission (i.e. 'omission-1') with the following IBI (i.e. interval of the first and second R-peak after the omission '1-2') and determined whether these differed between attention and delay conditions. A three-way ANOVA revealed significant effect of IBI (F(1,33) = 5.116, *p* = .030, n^2 = .008, BF_{incl} = 0.257), a significant effect of attention (F(1,33) = 4.170, *p* = .049, n^2 = 0.035, BF_{incl} = 4.912), a significant interaction of IBI and attention (F(1,33) = 4.555, *p* = .040, n^2 = 0.016, BF_{incl} = 0.574), and a significant interaction of delay and attention (F(1,33) = 3.979, *p* = .054, n^2 = 0.024, BF_{incl} = 0.812). The interaction of delay and IBI was not significant (F(1,33) = 0.125, *p* = .726, n^2 = 1.910e-4, BF_{incl} = 0.064), and the interaction of delay, IBI and attention was not significant (F(1,33) = 0.197, *p* = .660, n^2 = 2.942e-4, BF_{incl} = 0.045).

Posthoc tests of the IBI and attention interaction revealed a significant difference between the IBI 'omiss-1' during internal trials (M=841.282, SD=84.858) and IBI 'omiss-1' during external trials (M=831.659, SD=89.130; t(33) = 2.868, p_{holm} = .029) and a significant difference between the IBI '1-2' during internal trials (M=840.152, SD=86.261) and the IBI 'omiss-1' during external trials (t(33) = 2.762, p_{holm} = .033), and finally a significant difference between the IBI 'omiss-1' during external trials and the IBI '1-2' during external trials (M=838.208, SD=90.012; t(33) = -3.030, p_{holm} = .022). Therefore, revealing a cardiac deceleration following the omission during external trials only (as in Banellis & Cruse., 2020).

Posthoc tests of the attention and delay interaction revealed a significant difference between the IBI's during internal perceived asynchronous delay trials and the IBI's during external perceived asynchronous delay trials (t(33) = 2.846, p_{holm} = .036).

6.6 Heart rate variability

We analysed the standard deviation of the IBI's (SDRR) as a measure of heart rate variability. This revealed no significant HRV differences across attention (F(1,33) = 0.198, *p* = .659, n^2 = 0.002, BF_{incl} = 0.140) or delay trials (F(1,33) = 1.133, *p* =.295, n^2 = 0.013, BF_{10} = 0.229), as well as no significant attention and delay HRV interaction (F(1,33) = 0.536, *p* = .465, n^2 = 0.005, BF_{incl} = 0.048), further excluding heart-related confounds.

6.7 Multiverse controls

Supplementary Table 7. *Results of the baseline and CFA correction control analyses, using the significant time window of the effects with ICA CFA correction and without baseline correction (reported throughout the paper - in the black square, in bold). Green reflects significant results, although in italics if a different cluster polarity to the original result with ICA CFA correction and no baseline correction. Orange if marginally significant and red if not significant. 'R_ME_Delay' is the R-locked/pre-omission main effect of delay. 'R_ME_Attention' is the R-locked/pre-omission main effect of attention. 'Omiss_ME_Delay' is the omission-locked main effect of delay. 'Omiss_Int_AttAware' is the omission-locked interaction of attention with interoceptive awareness, with 'Att_HighAware(SynchOnly)' reflecting the simple/attention effect in high awareness participants and 'Att_LowAware(SynchOnly)' reflecting the simple/attention effect in low awareness participants only (in perceived synchronous trials only). 'AEP_154-209_HighPerceivers' is the first AEP effect of perceived synchrony and 'AEP_209-289_HighPerceivers' is the following AEP effect of perceived synchrony, both in high heartbeat perceivers* only.

	R_ME_Delay	**R_ME_Attention**	**Omiss_ME_Delay**	**Omiss_Int_AttAware**	**Att_HighAware(SynchOnly)**	**Att_LowAware(SynchOnly)**	**AEP_154-209_HighPerceivers**	**AEP_209-289_HighPerceivers**
ICACFA_-100-0Base	pos p=.001, neg p=.004	No sig clusters	pos p=.004	No sig clusters	N/A	N/A	pos p=.012	pos p=.003
ICACFA_-150--50Base	pos p=.001, neg p=.002	neg p=.021	pos p=.010	marg pos=.026	N/A	N/A	pos p=.016	pos p=.009
ICACFA_NoBase	**pos p=.024**	**neg p=.013**	**pos p=.022**	**pos p=.014**	**neg p=.019**	**No clusters**	**pos p=.021**	**pos p=.007**
NoICACFA_-100-0Base	pos p=.001, neg p=.001	No sig clusters	pos p=.001	No sig clusters	N/A	N/A	marg pos p=.025	pos p=.013
NoICACFA_-150--50Base	pos p=.001, neg p=.001	marg neg p=.027	pos p=.006	pos p=.022	*sig pos =.005*	No sig clusters	No sig clusters	marg pos p=.029
NoICACFA_NoBase	pos p=.005, neg p=.019	neg p=.005, marg pos p=.028	pos p=.010	pos p=.009	*sig pos=.016*	No sig clusters	pos p=.023	pos p=.011

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