# Interoception in Health and Disease

by

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Who knew that my undergraduate program director would receive an email from me asking him to stop using black backgrounds on his PowerPoints because it makes it really hard to see on a print-out of the slides. And who knew he would continue to find me bearable, write a letter of recommendation to Lorimer, and even commit to being as involved as needed on the next chapter, either behind the scenes, or as a supervisor. Turns out, many would know it, if they know Dr. Mark Kohler. A national treasure.

For those that know Prof. Lorimer Moseley, they just know how exceptional he is at what he does - I don’t need to make that case here. But something I was so lucky to learn was also how invested he is in his student’s well-being. I understand that this isn’t always the case from a primary supervisor unfortunately. But having Lorimer support me throughout this degree by regularly but not intrusively checking in on my mental health, something he knew could debilitate me in disastrous ways, is something I now look back on as being integral to me getting to where I am today.

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**Declaration**

I, Erica Wilkinson, declare that this thesis presents work carried out by myself and does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; to the best of my knowledge, it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, are clearly acknowledged.



Erica M. Wilkinson
06/12/2023

## Preface

This thesis is organised in four stand-alone chapters that can be read independently.

*Chapter One* introduces the thesis and provides a background of the literature relevant to interoception, its importance for general health, how it is associated with pathology, and lastly how interoception is altered in chronic pain conditions. *Chapter Two* is a systematic review and meta-analysis of the literature of the heartbeat evoked potential, as a marker of interoception, in health and disease. This review is formatted for, and under review for publication at *Imaging Neuroscience*. *Chapter Three* is a cross-sectional observational online survey that investigated the subjective appraisal of an individual's interoceptive awareness, and its relationship to the impact of pain experienced, across chronic pain conditions. This study is formatted for submission to *Journal of Pain*. *Chapter Four* discusses the totality of findings of the master thesis, its implications, and directions for future research. Each chapter is presented with its own independent reference list for consistency. Further, any supplementary material is either attached to the relevant chapter or to the end of the thesis, when appropriate.

Ethics was granted by the University of South Australia Human Research Ethics Committee for the cross-sectional study in *Chapter Three* (Ethics ID 203294; see *Appendix 5*). The studies undertaken in *Chapter Two* and *Three* were registered and this is indicated within each Chapter with the relevant hyperlinks. As both *Chapter Two* and *Chapter Three* are under review, no formal permission is required to reproduce it in this thesis.

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## List of Abbreviations

AD Alzheimer's disease
AIC Akaike information criterion
ANOVA Analysis of variance
ARTEM-IS Agreed Reporting Template for EEG Methodology - International Standard for documenting studies on Event-Related Potentials
BIC Bayesian information criterion
BP Blood pressure
BPI Brief Pain Inventory
BPQ Body Perception Questionnaire
CA Common average
CFA Cardiac field artefact
CHERRIES Checklist for Reporting Results of Internet E-Surveys
CI Confidence interval
CM Chronic musculoskeletal pain
CMA Comprehensive meta-analysis software
CR Complex regional pain syndrome
CRPS Complex regional pain syndrome
CSI Central sensitisation inventory
DASS Depression, Anxiety and Stress Scale
DSM Diagnostic and Statistical Manual of Mental Disorders
EC Eyes-closed
ECG Electrocardiography
EEG Electroencephalography
EO Eyes-open
EOG Electrooculography
ERP Event related potential
FIQ-R Fibromyalgia Impact Questionnaire - Revised
FIS Fronto-insular stroke
FM Fibromyalgia
FTD Fronto-temporal dementia
GAD Generalised anxiety disorder
HC Healthy control
HCT Heartbeat counting task
HEP Heartbeat evoked potential
HTT Heartbeat tracking task
IA Interoceptive accuracy
IBS Inflammatory bowel disease
ICA Independent components analysis

ICD International Classification of Diseases

IP Internet protocol

IQR Interquartile range

IRB Institutional review board

MA Mean average

MAIA Multidimensional Assessment of Interoceptive Awareness

MANOVA Multivariate analysis of variance

MATLAB Matrix laboratory

MDD Major depressive disorder

MEG Magnetoencephalography

OCD Obsessive compulsive disorder

OSF Open Science Framework

PANAS Positive Affect Negative Affect Scale

PCS Pain Catastrophising Scale

PICO Patient/population, intervention, comparison, and outcomes

PPI Pre-pulse inhibition

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO

PSQI Pittsburgh Sleep Quality Index

PTSD Post-traumatic stress disorder

REML Restricted maximum likelihood

SD Standard deviation

SE Standard error

SIQ Symptom Impact Questionnaire

SMD Standardised mean difference

STROBE Strengthening the Reporting of Observational studies in Epidemiology

VR Virtual reality

**Summary**

This thesis examines interoception, defined as the perception and integration of internal bodily signals, across clinical populations using both neural and subjective markers. The heartbeat evoked potential (HEP) is an implicit neural indicator of cardiac interoception that has become increasingly used in research of clinical populations. Interoceptive sensibility is the subjective self-report of one's interoceptive awareness and often includes questions related to perceptions of internal sensations such as heartbeats. *Chapter One* introduces the thesis and provides a background of the literature relevant to interoception, its importance for general health, how it is associated with pathology, and lastly how interoception is altered in chronic pain conditions. *Chapter Two* investigates the heartbeat evoked potential (HEP), an implicit neural indicator of cardiac interoception, through a systematic review and multilevel meta-analysis. Psychiatric, neurological, and cardiovascular conditions compared to healthy controls were included in the meta-analysis. Results demonstrated reduced HEP amplitude in neurological and cardiovascular groups but not psychiatric groups, indicating potential interoceptive deficits in some but not all disorders. However, methodological inconsistencies limit conclusions and underscore the need for standardised HEP protocols. *Chapter Three* is a cross-sectional observational online survey that investigates the subjective appraisal of an individual's interoceptive awareness, and its relationship to the impact of pain experienced, across chronic pain conditions. Findings reveal a positive association between pain impact and sensibility overall. This relationship was strongest for fibromyalgia and chronic musculoskeletal pain groups but weakest for complex regional pain syndrome. Variability hints at distinct mechanisms disrupting localised versus widespread bodily representations. Finally, *Chapter Four* synthesises overall findings, methodological implications, future research implications of this work, and presents potential clinical applications of interoceptive-based interventions.

# Chapter One

*“It makes sense to regard feelings from the body as the most primal feelings. We feel them all of the time, and they underlie most of our emotional feelings, if not all.”*

A.D. Bud Craig, 2014

## 1.1 What is interoception?

Interoception is currently regarded as a physiological representation of the state of the body that integrates the interpretation of internal and external signals within a cognitive/emotional context and plays an important role in homeostatic and behavioural regulation (Berntson & Khalsa, 2021; Chen et al., 2021; A. D. Craig, 2003; Khalsa et al., 2018). What we report in terms of our subjective bodily feelings and what is happening inside of our body can be captured by two distinct facets of interoception: the bodily changes we are consciously aware of and those we are not (Khalsa & Lapidus, 2016; Khoury et al., 2018). The biological processes through which interoception occurs are largely subconscious. Conversely, the internal sensations that we can consciously perceive, such as a racing heartbeat, can prompt us to take voluntary action.

The earliest literature suggested interoception (or more specifically "*interoceptors*" in its inception; Sherrington, 1906) was confined to the sole perception of the viscera (Airapetyantz & Bykov, 1945; Freeman & Sharp, 1941; Mogdenovich, 1941). Later, the definition expanded to a more integrated and bidirectional view of the body and brain, extending the interoceptive system to include thermoreceptors and small-diameter neurons (C-fibres and Aδ fibres) most obviously implicated in nociception (A. D. Craig, 2002; A. D. B. Craig, 2009; Critchley & Harrison, 2013; Damasio, 1999, 1999; Khalsa et al., 2018). Such neurons situated in the tissues provide a potential link between biological processes and patient-reported clinical experience.

In clinical settings, health providers frequently check in on a patient's overall wellbeing by asking *"how are you feeling?"*. Although interoceptive mechanisms largely operate below awareness, this question prompts introspection regarding bodily sensations that may otherwise go unnoticed, thereby linking our subjective appraisals to bodily events that are not directly observable.

## 1.2 Why is interoception important?

As a species, the ability of the brain to monitor the body is essential for survival. This momentary monitoring is required to adapt to changing environments and conditions. To maintain optimal health, the body must be regulated. While sometimes this process happens completely outside of our awareness (e.g. monitoring hormone levels), it must also be able to penetrate our awareness because it is this awareness – this *feeling we have* – that makes

us do something (e.g. to put on a jumper when we feel cold). This highlights the need for interoception to work at both levels of awareness and invariably ties interoception to homeostasis (Stephan et al., 2016). Human survival relies on homeostasis, a process that maintains the physiological mechanisms of the body within an optimal range. Complementary to homeostasis, allostasis refers to the necessary continuous forecasting of what will happen next in order to proactively regulate the body (Sterling & Eyer, 1988). This includes the regulation of vital functions such as body temperature, oxygen saturation, and blood pressure. Such processes require accurate inferences about the interoceptive state of the body (Barrett & Simmons, 2015; Petzschner et al., 2021; Quigley et al., 2021; Stephan et al., 2016), and together, this precise set of bidirectional feedback arrangements is most fundamental to life. In this sense, the state of homeostasis is synonymous with health – adapting to changing internal and external conditions while maintaining physiological integrity of the body. Consequently, dysfunction in homeostatic regulation can manifest as acute and chronic illnesses.

After eating, one may experience stomach cramps or other forms of gastrointestinal distress, which create a subjective sense of discomfort following a meal. Even if the food was safe to consume, your body may be signalling gastrointestinal distress, perhaps a "*gut feeling*" that you should vomit. Such interoceptive reactions can occur due to past contexts such as food poisoning, overeating, or other learned associations that signal illness. Whether warranted or not, the body and brain share the same goal of avoiding perceived threats through heightened unpleasant bodily signals. Given the potential monitoring role of interoception in the body, if interoception is disrupted, the homeostatic regulation of the body is also disrupted. Such aberrations can potentially have a systemic impact (Bonaz et al., 2021), as evidenced by clinical conditions such as inflammatory bowel syndrome (IBS) or diabetes. In the case of IBS, if we rely on signals from the gut and the gut is perpetually inflamed, it is possible that the disruption of interoceptive communication perpetuates the condition (Funaba et al., 2021; Holzer, 2022). Similarly, in diabetes, reduced awareness of internal cues, such as hypoglycaemia symptoms, can delay compensatory actions, exacerbating metabolic dysregulation (Martín-Timón & del Cañizo-Gómez, 2015; Yeoh et al., 2015).

The idea that past experiences shape our interoceptive system is exemplified in the case of adverse childhood experiences (ACEs). For example, there is compelling evidence that ACEs, such as abuse and neglect, affect how interoceptive signals are interpreted (Kolacz et al., 2019; Schmitz et al., 2023). This idea is also consistent with the Polyvagal Theory

(Porges, 1995) which proposes that the evolution of the autonomic nervous system allows for adaptive responses to threat. However, the Polyvagal Theory has received repeated criticism for relying on unfounded evolutionary assumptions regarding vagal pathways and the oversimplification of neural control of the autonomic nervous system (Beauchaine et al., 2019; Grossman, 2023; Monteiro et al., 2018; Neuhuber & Berthoud, 2022). Early life stress due to ACEs may lead to a dominant sympathetic state biased towards hypervigilance. Abnormal interoceptive development stemming from ACEs has been found to implicate cortical areas assumed to be responsible for interoceptive functions, such as the insula and anterior cingulate cortex (Harshaw, 2015) and to contribute to significant health vulnerabilities later in life (Fava et al., 2023; Guidi et al., 2021).

However, emerging data suggest that interoception has an important influence on the impact of a disease or disorder (Bonaz et al., 2021; Chen et al., 2021). An unresolved question is how important is one's perceived awareness of bodily sensations? One situation in which this is particularly relevant is that of a persistent pain state, in which pain may persist beyond what can be explained by tissue pathology alone, disrupting homeostasis and multiple systems. Furthermore, congenital insensitivity to pain[1] – by which fine diameter neurones in the tissues of the body lack an ion channel critical for response to dangerous stimuli - highlights the interoceptive foundation of pain, which bidirectionally informs the brain and body about safety (Melzack & Wall, 1984). In the instance of chronic pain, interoceptive information associated with the subjective feeling of pain may become dysregulated, despite the absence of tissue damage. However, persistent pain continues to be associated with disruption of the interoceptive system. This suggests that, in chronic pain, the brain may produce a feeling or experience of pain in the absence of sensory input, indicating a true threat to body tissues. Given the potential impact of perceived awareness of the experience of pain, accurately measuring interoceptive processing is critical.

## 1.3 How is interoception assessed?

Despite the continuous and largely unconscious monitoring of internal signals, we can intentionally direct attention to signals such as the heartbeat, which is most commonly implemented in research settings to assess interoceptive accuracy. However, the ability to

[1] This term is actually fallacious: people with this condition do not feel pain, therefore they cannot be insensitive to it. A more accurate term would be ‘congenital insensitivity to tissue-threatening stimuli’ (Cohen et al., 2022).

consciously focus on internal signals does not imply that they are not normally monitored subconsciously. For example, interoceptive signals like breathing are constantly tracked below consciousness even if they can be intentionally attended to.

### 1.3.1 Subjective markers

Self-report questionnaires of interoception, also known as interoceptive sensibility, are a common approach for assessing interoception (Desmedt et al., 2022). They often ask questions related to perceptions of internal sensations such as heartbeats, respiration, feelings of hunger and thirst, and bladder fullness. Tapping into multiple aspects of interoceptive experience provides a more comprehensive picture of an individual's awareness of internal states. As such, many questionnaires also include items related to an individual's awareness of their emotional state.

Assessments of interoceptive sensibility provide proximal, easy-to-administer, and subjective assessments of an individual's perceived interoceptive ability. Given their subjective nature, self-reports are susceptible to response biases, where an individual may underestimate or overestimate their interoceptive sensibility (Garfinkel et al., 2015; Vig, Köteles & Ferentzi, 2022). Nevertheless, this subjectivity is inherent in the construct into which these questionnaires aim to tap; they seek to quantify the introspective evaluation of one's subjective appraisal rather than an objective assessment of their accuracy.

#### Porges' Body Perception Questionnaire

The Body Perception Questionnaire (BPQ; Porges, 1993) assesses individual differences in body awareness, including visceral and autonomic sensations. Participants are asked to rate how often they perceive different sensations to assess their general tendency to sense interoceptive processes within the body. Cabrera et al. (2018) found the BPQ to have good internal consistency (ω = .77 to .96) and test-retest reliability (ICC = .96 to .99). The authors also demonstrated that higher BPQ scores correlate with psychopathology, where higher self-reported bodily awareness is associated with a psychiatric diagnosis.

Sample items from the BPQ Short Form include the following:

*"[I am aware of] how hard my heart is beating."* (Item 25)

*"I have difficulty coordinating breathing and eating."* (Item 27)

Mehling's Multidimensional Assessment of Interoceptive Awareness

The Multidimensional Assessment of Interoceptive Awareness (MAIA; Mehling et al., 2018) aims to evaluate the different facets of interoception across eight subscales. The MAIA has good internal consistency ($\alpha$ = 0.66-0.87) (Mehling et al., 2012) and reliability (ICC = 0.66-0.87) (Mehling et al., 2012). Purported to tap into both adaptive and maladaptive aspects of interoception, the MAIA may elucidate unique interoceptive processes across health conditions.

The eight subscales of the MAIA include the following:

1. *Noticing: Awareness of uncomfortable, comfortable, and neutral body sensations*
2. *Not-Distracting: Tendency not to ignore or distract oneself from sensations of pain or discomfort*
3. *Not-Worrying: Tendency not to worry or experience emotional distress with sensations of pain or discomfort*
4. *Attention Regulation: Ability to sustain and control attention to body sensations*
5. *Emotional Awareness: Awareness of the connection between body sensations and emotional states*
6. *Self-Regulation: Ability to regulate distress by attention to body sensations*
7. *Body Listening: Active listening to the body for insight*
8. *Trusting: Experience of one's body as safe and trustworthy*

Sample items from the MAIA include the following:

*"I push feelings of discomfort away by focusing on something"* (Item 9)

*"I feel my body is a safe place."* (Item 36)

A second approach to capture interoception is behavioural assessment. The most widely administered behavioural task is the Heartbeat Counting Task (Schandry, 1981) which requires an individual to count their heartbeat for an unidentified length of time across multiple trials (Montoya et al., 1993; Pollatos et al., 2005; Pollatos & Schandry, 2004; Schandry et al., 1986). An individual's accuracy score is calculated as the difference between the reported number of heartbeats and the actual number of heartbeats, as assessed by electrocardiography.

Variations in the Heartbeat Counting Task exist. The heartbeat tapping task replaces the instruction of counting heartbeats with physical tapping in response to each felt heartbeat (Canales-Johnson et al., 2015; Garcia-Cordero et al., 2016; Sedeno et al., 2014; Yoris et al., 2015, 2018). The heartbeat synchronisation task requires the participant to judge whether a sequence of tones (or light flashes) is synchronous with their heartbeat (Brener & Kluvitse, 1988; Critchley et al., 2004; Katkin et al., 1991). Similarly, the heartbeat discrimination task requires the participant to judge whether an audio recording of a heartbeat is their own (Azevedo et al., 2016). Not only are behavioural assessments of interoception weakly associated with each other (Hickman et al., 2020), but they have also been found to lack consistency within the same cohort (Pennebaker & Hoover, 1984).

Despite being seemingly better aligned with interoceptive function than a questionnaire, task-oriented assessments risk interrogating more than interoception alone (Brener & Ring, 2016; Khalsa & Lapidus, 2016; Phillips et al., 1999; Ring & Brener, 2018). These behavioural assessments have drawn criticism regarding their validity (tasks may require extended attention, short-term memory, or frequent motor responses), potential bias (e.g. a participant's prior knowledge of their resting heart rate, body position during assessment, and possible social desirability bias), and conflating interoception with other cognitive abilities (Ainley et al., 2020; Brener & Ring, 2016; Corneille et al., 2020; Desmedt et al., 2018, 2022; Knapp-Kline et al., 2021; Legrand et al., 2021; Murphy, 2023, p. 202; Murphy et al., 2019; Phillips et al., 1999; Ring et al., 2015; Windmann et al., 1999; Zamariola et al., 2018; Zimprich et al., 2020). Such issues have led to a consensus that these assessments capture more than just interoception. Assessments that avoid these limitations may provide a more proximal marker for interoceptive function.

### 1.3.2 Neurophysiological markers

Unlike subjective assessments of interoception, neurophysiological correlates of cardiac interoception offer an objective, implicit marker of interoception, as they do not require conscious awareness of internal sensations nor conscious action to report sensations (Simmons et al., 2013; Wiebking & Northoff, 2015). An important caveat when considering objective assessments of interoception is the complexity of interoceptive processing, which suggests that multiple brain regions and networks are involved in interoceptive awareness (Khalsa et al., 2009; Kleckner et al., 2017).

Electroencephalography (EEG) is a physiological technique that noninvasively records cortical activity through electrodes placed on the scalp. Different brain states and rhythmic activity can be captured through EEG. Distinct frequency bands in the EEG signals have been implicated in multiple interoceptive tasks. Villena-Gonzalez et al. (2017) found greater alpha power (8-12 Hz) over parieto-occipital regions during an interoceptive heart-monitoring task than during a visual task. Alpha power was moderately correlated with interoceptive accuracy. Canales-Johnson et al. (2015) showed increased gamma phase synchrony (30-45 Hz) following heartbeat feedback, but only in those with agreement between interoceptive performance and metacognitive awareness. These findings indicate that alpha rhythms over parietal and occipital areas support interoceptive attention, while gamma oscillations may reflect the integration of interoceptive signals with conscious awareness.

The heartbeat evoked potential (HEP) is a marker of brain activity time-locked to the cardiac cycle using EEG (Schandry et al., 1986) (see *Figure 1*). As such, HEP is considered a physiological signal of a brain-body connection. This is distinct from the mind-body connection, which is usually used to capture one's awareness of their body. Spatially, HEP is thought to be modulated within frontal (Canales-Johnson et al., 2015; Park et al., 2016), central (Montoya et al., 1993; Petzschner et al., 2019), and parietal regions (Dirlich et al., 1998; Pollatos & Schandry, 2004; Sel et al., 2017). This supports neural findings linking HEP modulation to the insula (Babo-Rebelo et al., 2016; Pollatos et al., 2005), anterior cingulate cortex (Critchley et al., 2004), amygdala (Kern et al., 2013; Park et al., 2018), and somatosensory cortex (Kern et al., 2013; Park et al., 2018; Pollatos et al., 2005; Schandry et al., 1986). Additionally, HEP appears to be altered in various clinical diagnoses, and may offer a clinically meaningful index of interoceptive function (Petzschner et al., 2019). Additional research examining the interoceptive system through top-down or bottom-up mechanisms will likely offer further insights on its disrupted nature in clinical conditions. As such, studying systemic disruptions in patient populations may reveal specific mechanisms, and this may ultimately provide insights into the underlying neural processes that could inform measurement and diagnostic approaches.

HEP offers several advantages over other methods for assessing interoception. Self-report assessments, such as the BPQ, are limited by subjectivity and metacognitive awareness. Behavioural tests, such as the Heartbeat Counting Task, reflect performance rather than perception. In contrast, HEP provides an objective neural marker of interoceptive processing

that does not rely on metacognition or task performance. As a physiological indicator that is time-locked to each heartbeat, HEP captures real-time fluctuations in internal body awareness. This offers superior temporal resolution compared with fMRI methods for mapping interoception. HEP also demonstrates good test-retest reliability and correspondence with other interoceptive assessments (Pollatos & Schandry, 2004; Schandry et al., 1986). Given these strengths, HEP represents a promising tool for elucidating interoceptive processes and how they may be disrupted in clinical conditions. By objectively indexing interoceptive function, HEP may offer insight into the precise nature of interoceptive disturbances underlying conditions, such as chronic pain disorders, anxiety, and depression

Contemporary approaches to interoception centre on a predictive system whereby the brain generates predictions about expected internal body signals. Prediction errors between anticipated and actual interoceptive signals are then detected and used to update the internal models of the brain (Clark & Chalmers, 1998; Seth & Friston, 2016; Van den Bergh et al., 2017). This thesis evaluates interoception through the lens of active inference by applying predictive coding principles to how the brain infers the current state of the body (Allen, 2020; Barrett & Simmons, 2015; Seth, 2013, 2016). Within this framework, the brain holds generative models that represent the expected patterns of physiological sensations, such as heartbeats. HEP can be conceptualised as reflecting a comparison process between the brain's predicted heartbeat signal and the actual incoming heartbeat sensation. When a mismatch occurs between the prediction and sensory input, prediction error signals are generated to update the brain's internal models of cardiovascular state. Examining HEP provides a window into this continuous interplay between top-down predictive signals and bottom-up interoceptive prediction errors.

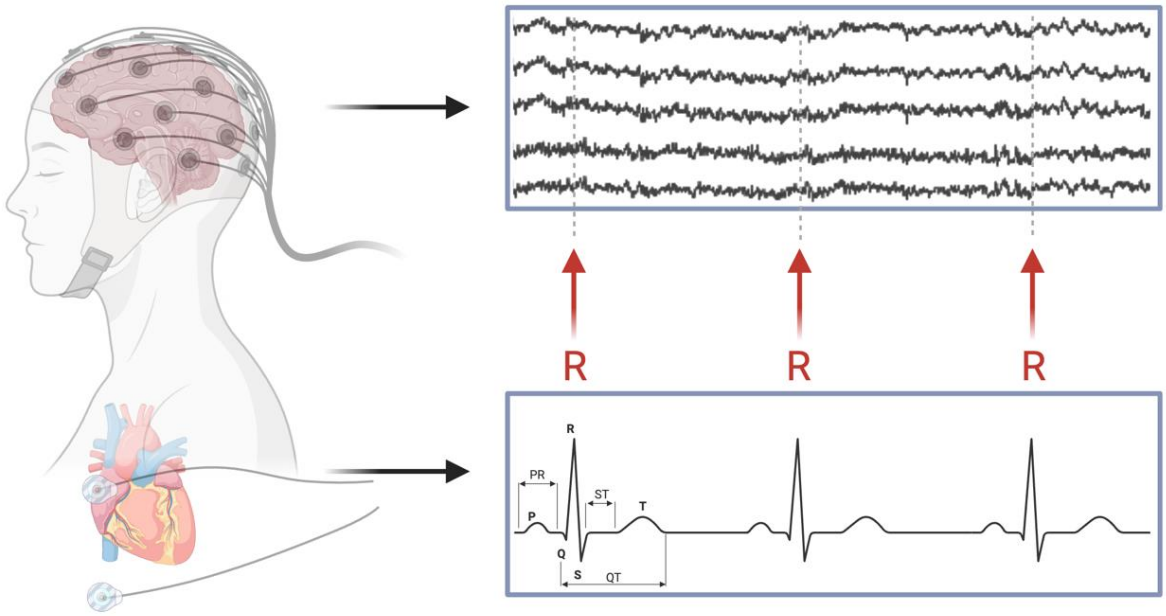



**Figure 2. Depiction of the physiological components of the heartbeat evoked potential.**

**Note:** Electroencephalography (EEG) and electrocardiography (ECG) electrodes concurrently monitor the heart and brain. The offline EEG is time-locked to the R-wave present in the ECG data.

## 1.4 Rationale for Study One

Accumulating evidence suggests that interoceptive processing may be disrupted in a range of psychiatric and medical conditions (Di Lernia et al., 2016, 2020; Pollatos et al., 2009, p. 200; Taylor et al., 2021). Disrupted interoceptive processing has also been observed in individuals with autism, dementia, and chronic pain (Birba et al., 2022; Garfinkel et al., 2016; Khalsa et al., 2018; Solcà et al., 2020). These interoceptive disturbances are thought to contribute to key symptoms of these disorders. A systematic evaluation and quantitative synthesis of the existing literature on HEP in clinical groups compared with healthy individuals will provide clarity regarding the disruption of HEP across conditions.

Self-report and task-oriented assessments of interoception have significant reliability and validity problems. Self-reports using questionnaires are subjective and metacognitively limited. Behavioural tests assess performance rather than perception, are susceptible to response biases, and show poor test-retest reliability (Garfinkel et al., 2015). These limitations undermine the findings using questionnaires and tasks to assess interoceptive deficits and underscore the need for more objective neural markers for interoceptive functioning (Desmedt et al., 2022; Ferentzi et al., 2018; Ring & Brener, 2018).

HEP has emerged as a promising objective marker for interoception. However, it remains unclear how HEP is altered under different clinical conditions. Furthermore, a consistent aspect of the emerging HEP data is its methodological inconsistency; different studies report different aspects of HEP, collecting data under different conditions and in different settings with different approaches. Therefore, it is imperative to systematically review and, if appropriate, perform a meta-analysis to determine the current state of evidence regarding HEP abnormalities across clinical disorders. This may provide guidance for future research by enabling enhanced measurement, diagnosis, and treatment.

**Study 1** aimed to determine whether and to what extent the amplitude of HEP differed between people with a clinically diagnosed condition and a healthy control group.

**Study 1** also aimed to systematically characterise the methodological parameters used to record and analyse HEP to date in the literature.

**Study 1** is presented as a submitted paper in **Chapter Two**, titled: Interoception in health and disease: A meta-analytical review of the neurophysiological properties of the heartbeat evoked potential.

## 1.5 Rationale for Study Two

Clinicians routinely ask patients "*how are you doing?*" before evaluating their health status. However, the response is rarely probed deeper, in favour of biomedical metrics. Given the interlinked nature of interoception and chronic pain, evaluating patients' subjective bodily experiences may provide critical insights into how chronic pain conditions impact health and wellbeing. Consequently, purely biomedical models fail to capture the multidimensional nature of chronic pain. Examining interoceptive processing in individuals with chronic pain may elucidate the links between physical sensations, cognitive-affective appraisals, and pain experience.

Furthermore, specific diagnoses demonstrate distinct impacts owing to their unique mechanisms. Fibromyalgia is associated with widespread pain, tenderness, fatigue, and altered emotional processing (Arnold et al., 2016). Individuals with fibromyalgia demonstrate both a decreased sensitivity to bodily cues (Duschek et al., 2017; Martinez et al., 2018) and an increased response to non-noxious sensations (Sluka & Clauw, 2016). In contrast, complex regional pain syndrome is characterised by localised limb pain and autonomic

abnormalities. Patients exhibit distorted body representations, proprioceptive deficits, and an inability to integrate exteroceptive visual cues with interoceptive signals from the affected limb (Lewis & Schweinhardt, 2012).

Ultimately, a biopsychosocial framework that integrates biological, psychological, and subjective factors is essential for understanding multidimensional pain experiences (Raja et al., 2020). Examining the differences in interoceptive beliefs across populations may inform patient-tailored mind-body interventions. For instance, interoceptive training may benefit fibromyalgia (Bravo et al., 2019; Tahran et al., 2023), whereas sensory retraining approaches may be more appropriate for treating complex regional pain syndrome (Coggins et al., 2023; Halicka et al., 2020; Lewis et al., 2011). Overall, research on diagnostic-specific interoceptive disruptions may provide insights into the lived experience of chronic pain and may ultimately inform interoception-focused interventions to improve mind-body connections and wellbeing in chronic pain populations.

**Study 2** aimed to determine whether self-reported interoception, known as interoceptive sensibility, is associated with pain impact in people from four separate groups: people living with fibromyalgia, people living with complex regional pain syndrome, people living with another chronic musculoskeletal syndrome, and healthy controls.

**Study 2** aimed to characterise the relationship between independent demographic variables, wellbeing, affect, pain, and interoceptive sensibility using descriptive and regression analysis.

**Study 2** is presented as a submitted paper in **Chapter Three**, titled: Minding the body: Interoceptive sensibility is associated with pain impact in people with chronic pain disorders.

## 1.6 Thesis Overview and Aims

This thesis consists of two studies: a systematic review and three-level meta-analysis (*Chapter Two*), and a cross-sectional observational survey (*Chapter Three*). Both the studies in this thesis have been formatted for publication. At the time of submission, *Chapter Two* was formatted for submission to *Imaging Neuroscience* and *Chapter Three* was formatted for submission to *PAIN*. *Chapter Two* discusses the state of the field of one physiological marker of interoception and presents, for the first time, systematic evidence of physiological interoceptive distinctions in individuals with psychiatric, neurological, and cardiovascular conditions. *Chapter Three* provides compelling evidence to suggest that how in tune people with chronic pain think they are with their body is associated with the impact

of their condition on their life. Finally, *Chapter Four* discusses the overall findings of this thesis, their implications for the field of interoception, and how they inform the direction of the field.

## 1.7 References


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# Chapter Two

# Interoception in health and disease: A meta-analytical review of the neurophysiological properties of the heartbeat evoked potential

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## Abstract

The heartbeat evoked potential (HEP) is considered a neurophysiological indicator of interoception. It has also been observed that various clinical conditions can disrupt interoceptive awareness, leading to the suggestion that HEP amplitudes could serve as valuable biomarkers of interoception. Nevertheless, there is limited understanding regarding how HEP is affected by different conditions and which parameters are most indicative of pathology. We synthesised the current evidence for abnormal HEP amplitudes across all available clinical subpopulations using a random-effects multilevel meta-analysis. We extracted latency window, reference, and scalp electrode topographies, and systematically characterised them across studies (OSF Doi: 10.17605/OSF.IO/TMQ3W). A subgroup analysis by diagnostic group revealed a significant effect in neurological ($g$ = -0.513) and cardiovascular ($g$ = -0.818) groups, indicative of reduced HEP amplitudes relative to healthy comparisons. There was no effect of psychiatric condition on HEP ($g$ = 0.049). HEP amplitude appears to be reduced in people with neurological or cardiovascular conditions but not in people with psychiatric conditions. However, methodological inconsistencies and shortcomings raise questions over the extent and nature of these observations.

## Introduction

The process by which the nervous system senses and interprets internal bodily signals is known as interoception (Khalsa et al., 2018). Interoception occurs via a constant bidirectional feed of bodily-state information to the brain and back again via numerous pathways within the peripheral and central nervous system (Ádám, 1998; Berntson & Khalsa, 2021; Seth & Friston, 2016). Many of these signals are processed without conscious awareness (Cameron, 2001), suggesting that interoception contributes to homeostatic maintenance in the midst of a constantly changing environment. At other times, an individual may be aware of a state change, such as the feeling of hunger, and may change their behaviour to regulate homeostatic processes, such as eating to replenish energy levels (Kleckner et al., 2017; Nave et al., 2020; Prilutski & Livneh, 2023; Shaffer et al., 2022; Sherrington, 1906).

Dysfunction of interoception is increasingly being recognised as an important component of various mental health conditions in part because interoception relates to how well individuals perceive, interpret, and regulate their internal bodily states (Barrett & Simmons, 2015; Brewer et al., 2021; Cameron, 2001; Coll et al., 2021; Craig, 2002; Damasio, 1999; Khalsa et al., 2018; Suksasilp & Garfinkel, 2022). Furthermore, medical conditions that have a psychological or psychiatric component, such as somatisation disorders and chronic pain conditions (e.g., Fibromyalgia and Complex Regional Pain Syndrome) are also associated with interoceptive dysfunction (Brewer et al., 2021; Pinto et al., 2023), as are neurological disorders (Bonaz et al., 2021; Migeot et al., 2022). Failures to appropriately anticipate and adapt to a change of internal state have been linked to affective processing in psychiatric and neurological disorders (Adams et al., 2022; Bonaz et al., 2021; Brewer et al., 2021; Nord & Garfinkel, 2022; Paulus et al., 2019), suggesting that the key role played by interoception in well-being underpins a need to consider its role in clinical presentations of various conditions.

The heartbeat evoked potential (HEP) is one promising candidate marker of interoception because it appears to reflect the cortical processing of the heartbeat but does not also rely on behavioural performance. The heart continuously and cyclically sends afferent signals to the brain along the vagus nerve via baroreceptors and mechanoreceptors (Gray et al., 2007; Park & Tallon-Baudry, 2014). These signals then, are thought to reflect changes in blood pressure within the aorta and carotid arteries, effectively encoding cardiac cycle oscillations and fluctuations of both timing and strength of heartbeats (Azzalini et al., 2019; Kern et al.,

2013; Park & Blanke, 2019). Contemporary theories propose that these ascending projections update brain-held models of the state of the heart; HEP is thus considered a marker of cardiac interoception (Park & Blanke, 2019). HEP is demonstrated by synchronising continuous brain activity (via electroencephalography; EEG) to the heartbeat (via electrocardiography; ECG) when time-locking to the R-peak of the cardiac cycle is treated as the stimulus in an event related potential paradigm. Most studies with a healthy cohort use a window between 200 ms to 650 ms after the R-peak (Dirlich et al., 1998; Kern et al., 2013; Montoya et al., 1993; Schandry et al., 1986) to reflect the distinct cardiac events of systole (approximately 200-300 ms after the R-peak) and diastole (approximately 500 ms or more after the R-peak).

The potential clinical utility of HEP as a neurophysiological marker of interoception is largely attributed to its implicit nature; it does not require the individual to be consciously aware of their heartbeat, nor even necessarily awake (Candia-Rivera et al., 2021; Lechinger et al., 2015). Although attention is not essential for the recording of HEP (Dirlich et al., 1998; Montoya et al., 1993), it is susceptible to modulations of attention (Petzschner et al., 2019), arousal (Luft & Bhattacharya, 2015), and pain (Shao et al., 2011), in addition to hunger (Schulz, Ferreira de Sa, et al., 2015), and altered motivation (Weitkunat & Schandry, 1990). The present study builds upon a previous meta-analysis (Coll et al., 2021) that established moderate to large effects of interoception on HEP amplitude. Specifically, the authors investigated the modulation of attention, interoceptive task performance, arousal, and clinical condition on HEP, outlining a range of findings pertaining to the relationship between interoception and its potential neural marker, HEP. Given the building literature suggesting interoception is disrupted in various clinical conditions, this may provide a marker of dysfunctional interoception at a neural level. Coll et al. demonstrated a moderate effect of clinical group on HEP ($g = 0.49$); however, a clear interpretation of this finding is lacking. A shortcoming of the review, however, was that HEP outcomes were determined across combined clinical conditions. This left the critical and clinically relevant question of whether and in what way HEP may characterise clinical groups unanswered. In this study, we used standard diagnostic classifications to cluster included conditions and multilevel meta-analyses to examine HEP outcomes in 21 studies of which 12 overlap with Coll et al.

The primary aim of this review was to determine whether, and to what extent, the amplitude of HEP differed between people with a clinically diagnosed condition and a healthy comparison group. The second aim of this review was to systematically characterise the

methodological parameters used to record and analyse HEP to date in the literature. We applied robust statistical models that account for within-study biases and dependencies (Song et al., 2020), heterogeneity, and small-study effects. Additionally, we aimed to provide a meaningful, clinically relevant outcome, through the integration of prediction intervals and subgroup analyses. These decisions are expected to assist the precision and confidence in the outcomes.

## Methods

### Data sources and search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines (Page et al., 2021). Prior to commencing the database searches, the International Prospective Register of the Systematic Reviews (PROSPERO) and Open Science Framework (OSF) were searched for registered protocols of the same or similar systematic review. No such protocols were identified on either PROSPERO or OSF. Therefore, prior to commencing our systematic review, a protocol was registered on 29th February 2020 on OSF (Doi: 10.17605/OSF.IO/TMQ3W). The PRISMA 2020 Checklist (Page et al., 2020) was completed and documented (see *Supplementary Material 1*). A sensitive search strategy was designed in accordance with the PICO framework (Schardt et al., 2007); the characteristics of the literature search and an example search (MEDLINE) are presented in *Table 1*. Searches, tailored to each database, were conducted in: MEDLINE (OvidSP), Cochrane (Cochrane Library), SCOPUS (Elsevier), Embase (OvidSP), EmCare (OvidSP), PsycINFO (OvidSP), and Web of Science (Clarivate Analytics) databases; see *Supplementary Material 3* for the full list of search strings for each database. All reference lists and citations of included studies were manually searched for further relevant studies that did not appear during the database searches. Final searches were conducted on 3rd November 2022.

### Study eligibility

Refer to *Table 1* for study inclusion and exclusion criteria.

**Table 1. Characteristics of the literature search**

| | |
|---|---|
| Databases | MEDLINE (OvidSP), Cochrane (Cochrane Library), SCOPUS (Elsevier), Embase (OvidSP), EmCare (OvidSP), PsycINFO (OvidSP), and Web of Science (Clarivate Analytics). |
| Language | No restrictions |
| Document type | Peer-reviewed empirical article |
| Inclusion criteria | Population: Human adults (≥18 years) with a clinical condition. Intervention: Interoceptive task performance as specified by the author. Comparison: A diagnosed group compared to a healthy state or a healthy comparison group. Outcome: A scalp-level HEP response. |
| Exclusion criteria | Animal studies, grey literature and secondary data, book chapters, dissertations, theoretical papers, conference materials |
| Keywords for literature search | See *Supplementary Material 2* for a full list of search strings for each database. Below is an example taken from the MEDLINE search: Evoked Potentials/,Event-Related Potentials, Heart Rate/, (Cardiac-afferent signal* or cardio-afferent signal* or Heart?beat-evoked potential? or heart?rate-evoked potential? or heart? beat?-evoked potential? or heart? Rate?-evoked potential? or Heart?beat-evoked response? or heart?rate-evoked response? or heart? beat?-evoked response? or heart? Rate?-evoked response?).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] ((Heart beat* or Heart?beat* or Heart rate* or Heart?rate or cardiac or cardio) adj3 (evoked potential? or evoked response? or event-related potential? or event related potential? or Evoked brain? Potential? or afferent signal* or scalp potential? or "Neural response? to")).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms], (amplitude? or latenc* or latent or wave* or magnitud*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |

## Article selection

Identified studies were uploaded to Covidence (www.covidence.org) where duplicates were removed automatically. Two independent reviewers (EMW, HGJ) screened titles and abstracts of all identified studies and excluded any clearly irrelevant studies. Relevant full-text articles were retrieved. The same reviewers independently reviewed the studies for eligibility based on a customised eligibility criteria form (see *Supplementary Material 3*). Any disagreements were resolved by discussion, or if necessary, through consultation with a third reviewer (CB).

## Risk of Bias assessment

A customised risk of bias form was constructed, based on relevant items from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE; Elm et al., 2007) checklist for cross-sectional studies (http://www.strobe-statement.org). The checklist was adapted to critically appraise each included study based on specific criteria relevant to the review objectives. For example, EEG-specific appraisal questions were

included in the customised risk of bias form based on the guidelines set out by Picton et al. (2000) and Keil et al. (2014) for recording event-related potentials and publication criteria (see *Figure 2*). This assessment was completed by two independent reviewers (EMW and HGJ) and disagreements were resolved by discussion, or if necessary, through consultation with a third reviewer (CB). No total score could be determined because the modified tool was not validated.

## Evaluation of the meta-analytic process

To critically evaluate the current meta-analysis, methodological appraisal questions regarding meta-analyses, suggested by Nakagawa et al. (2017), were followed and documented (see *Table 3*). This evaluation process also included the five recommendations for nonindependence reporting, suggested by Noble et al. (2017).

## Data extraction

Two independent reviewers (EMW, HGJ) used a piloted, customised form to extract data from eligible studies. The following items were extracted: (1) group-specific characteristics (type of clinical condition, sample size, demographic information of both clinical and healthy groups); (2) behavioural condition in which HEP was recorded (i.e., resting state or interoceptive task condition); (3) electrophysiological method used (EEG/ECG equipment used, pre-processing techniques, HEP measurement protocol); (4) quantitative outcome data for HEP parameters reported for both clinical and healthy groups. If additional information was required, authors were contacted a maximum of three times within a three-month time frame for responding; after which, the information was considered unretrievable.

A qualitative synthesis of the data was completed to determine the most common EEG pre-processing steps and analysis for HEP experiments. Where possible, HEP parameters were also extracted to gain a consensus of the best parameters to differentiate HEP between clinical groups and healthy comparison groups/state (see *Table 4* for full list of parameters extracted). A meta-analysis was performed to determine if HEP amplitude differences existed between clinical groups versus healthy controls. Quantitative outcomes were retrieved from each study, if available. If values given were not an exact value (e.g., a *p*-value of less than a threshold value), the author was contacted for exact values, and if the data could not be retrieved, the study was not included in the meta-analysis.

## Data analysis

All analyses were performed using R (R Core Team, 2021) using the metafor package (version 3.0.2) (Viechtbauer, 2010). The dataset and analysis code are available on OSF (Doi: 10.17605/OSF.IO/TMQ3W). *A priori*, we decided to transform all quantitative outcomes of HEP amplitude difference to a standardised mean difference (SMD) in order to produce comparable and clinically interpretable outcomes (Higgins et al., 2019; Lipsey & Wilson, 2001). As many included studies had small sample sizes, Hedge's *g* SMD was chosen as the appropriate SMD because it accounts for smaller study sample sizes ($n < 20$) which are vulnerable to overestimating true effect sizes (Hedges, 1981).

To assemble the data, effect estimates were calculated based on the reported quantitative outcomes (Cohen's *d*, mean and standard deviations, exact *p* values) and then all data were transformed to Hedge's g SMD using the metafor package in R. During data extraction it became apparent that some of the included studies were reporting effect sizes for multiple clinical conditions or task conditions combined. To account for the likely within-group correlation and potentially inflated Type 1 error rates (Fernández-Castilla et al., 2021), the *a priori* data analysis plan was updated by implementing a multilevel meta-analytic model. The multilevel meta-analytic model approach appropriately accounts for the within-study sampling and effect dependencies (Hox et al., 2017) and enables the analysis of variance between study effect sizes. Following the guidelines by Assink and Wibbelink (2016), a multilevel meta-analysis was performed. This required changes to the *a priori* planned assessment of heterogeneity.

To estimate heterogeneity, the Restricted Maximum-Likelihood (REML) estimator (Viechtbauer, 2005), the Q-test (Cochran, 1954), and the $I^2$ statistic (Higgins and Thompson, 2002; Moran et al., 2017) were used. To provide a clinically relevant interpretation, prediction intervals were also included in the meta-analysis reporting because it allows for the prediction of true effects in future settings (IntHout et al., 2016; Riley et al., 2011). To determine whether the within-study variance (Level 2) and between-study variance (Level 3) were significant, log-likelihood ratio tests were performed.

To determine whether HEP amplitude was influenced by task, it was decided *a priori* to include only tasks which required participants to deploy goal-directed (i.e., top-down) attention towards the heart; this included a heartbeat counting task or a resting state task that was explicitly stated that it was considered interoceptive. Therefore, the data were

classified by the following sub-groups: interoceptive or resting state. The interoceptive group included active tasks such as heartbeat counting, heartbeat tapping, or heartbeat discrimination tasks. The resting state group included HEP when eyes were open or closed, or during sleep.

## Subgroup and moderator analyses

To account for sample heterogeneity, a subgroup analysis was performed. The conditions were categorised in the following ways: The psychiatric subgroup was categorised as psychiatric if it met the criteria for a psychiatric disorder in the Diagnostic and Statistical Manual of Mental Disorders (2013). The neurological subgroup was categorised as neurological if it met the criteria for neurocognitive diseases of the nervous systems in the International Classification of Diseases (2022).

The cardiovascular subgroup included any diagnostic disease or condition directly related to the heart.

Two independent reviewers (EMW, HGJ) classified each condition as psychiatric, neurological, or cardiovascular based on the reported features that determined the diagnosis (e.g., Kumral et al. (2022) used a sample of people with atrial fibrillation diagnosed by a cardiologist). Secondly, as HEP amplitude was reported under active (interoceptive task) or passive (resting state) task conditions, a moderator analysis was performed to test for the effect of task condition on effect estimates.

## Analysis of publication bias

To check for publication bias, a funnel plot was used to visually inspect the relationship between average effect sizes and standard error (Nakagawa, Lagisz, et al., 2022). Testing for publication bias is predicated on three factors: (1) that negative or null findings are less likely to be published (e.g., the file-drawer problem); (2) that a high level of heterogeneity is accounted for (Macaskill et al., 2001; Moreno et al., 2009; Sterne et al., 2001); and (3) that non-independent effect sizes are accounted for. We predicted that this meta-analysis would not be impacted by the file-drawer problem given that non-significant findings of HEP differences between diagnostic and healthy comparisons still provide valuable information about the individual diagnostic condition and hence would be published.

High heterogeneity and non-independent effect sizes (within study dependencies) (Fernández-Castilla et al., 2021; Nakagawa & Santos, 2012), however, were predicted to

influence the robustness of the estimated results (Noble et al., 2017), resulting in the potential for tests of publication bias to fail (Macaskill et al., 2001; Moreno et al., 2009; Sterne et al., 2001). To account for these factors, a uni-moderator multilevel meta-regression was fitted by including the square root of the inverse of effective sample size as the moderating variable (Song et al., 2020). Multi-level meta-regression extends the existing regression-based methods (Egger's regression) by accounting for within-study dependencies of outcomes (Song et al., 2020).) and small-study effects (Macaskill et al., 2001; Moreno et al., 2009; Sterne et al., 2001). It included three levels of variance representation: Level 1: within study sampling variance; Level 2: within study variance of effect sizes; and Level 3: variance between studies.

## Results

### Data extraction

*Figure 1* illustrates the study selection process in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA; Page et al., 2021). From the 814 records identified from the searched databases, 473 duplicates were removed, and the titles and abstracts of the remaining 341 records were screened. A total of 323 records were excluded at title-abstract screening. The remaining 18 full texts were sought for retrieval and assessed for eligibility. At full-text screening, three records were excluded that did not include a healthy control group (Gray *et al.*, 2007; Judah *et al.*, 2018; Schulz *et al.*, 2020). Through citation screening, a further six articles were identified as eligible for inclusion, and full-texts were retrieved (Salamone *et al.*, 2018; Yoris *et al.*, 2018; de la Fuente *et al.*, 2019; Garcia-Cordero et al., 2016; Schulz et al., 2022; Solcà *et al.*, 2020). A total of 21 studies met the inclusion criteria and were included for review. After contacting 12 authors for additional information, all 21 studies were included in the meta-analysis.

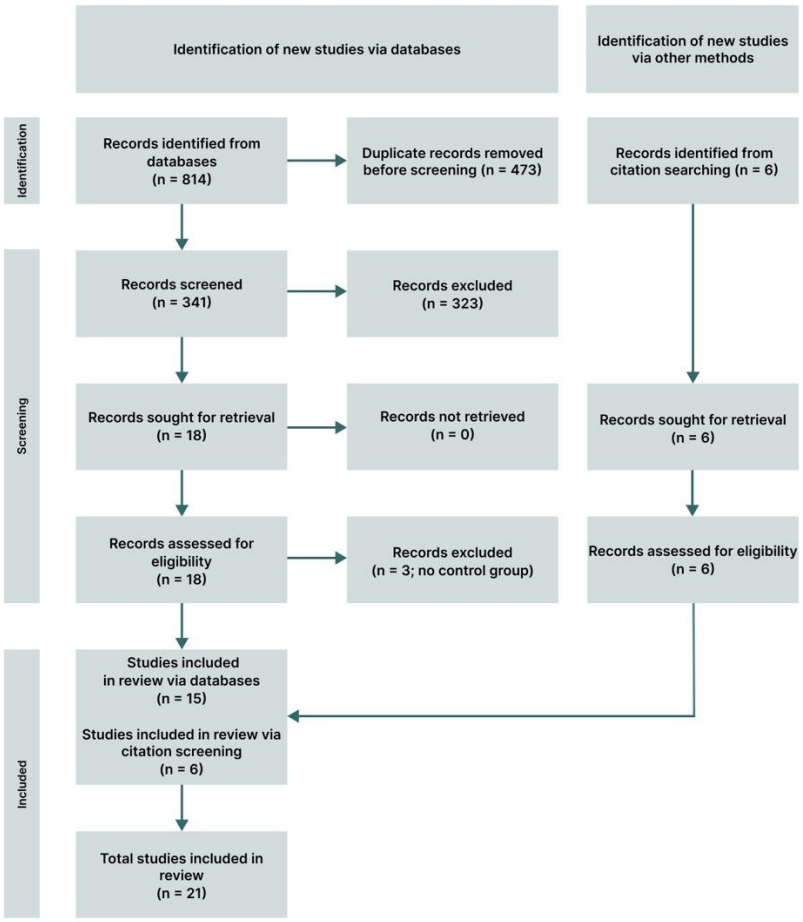



**Figure 1. PRISMA flow chart of included studies**

## Study characteristics

Of the 21 included studies (see *Table 2* for summary of included studies), 18 were cross-sectional between-group designs. The remaining three studies included a case control study that took place in a hospital (Müller et al., 2015), a mixed group, prospective longitudinal cohort study that took place over three time points (Salamone et al., 2020), and a randomised, double-blind placebo-controlled trial, of which only the placebo arm was included in the current review (Schmitz et al., 2020). Overall, the sample size between the total clinical sample (n=607) and healthy sample (n=597) was balanced. The sample sizes for the pooled clinical conditions were as follows: psychiatric versus healthy comparison 360:331; neurological versus healthy comparison 150:153; and cardiovascular versus healthy comparison 97:113. The 21 studies and their demographic information are displayed in *Table 2*. A synthesis of the EEG methodology and HEP parameters is presented in *Table 4.*

### Non-independent experimental designs

Four studies (Birba et al., 2022; Garcia-Cordero *et al.*, 2016; Schulz et al., 2022; Yoris *et al.*, 2017) included multiple clinical groups in their analysis with a shared healthy control group. Two studies (Perogamvros et al., 2019; Schulz, Koster, et al., 2015) included multiple task conditions, and one study (Salamone et al., 2020) included multiple time-points of HEP recording. Therefore, a total of 29 effect estimates from 21 studies were included in the analysis.

**Table 2. Study Characteristics**

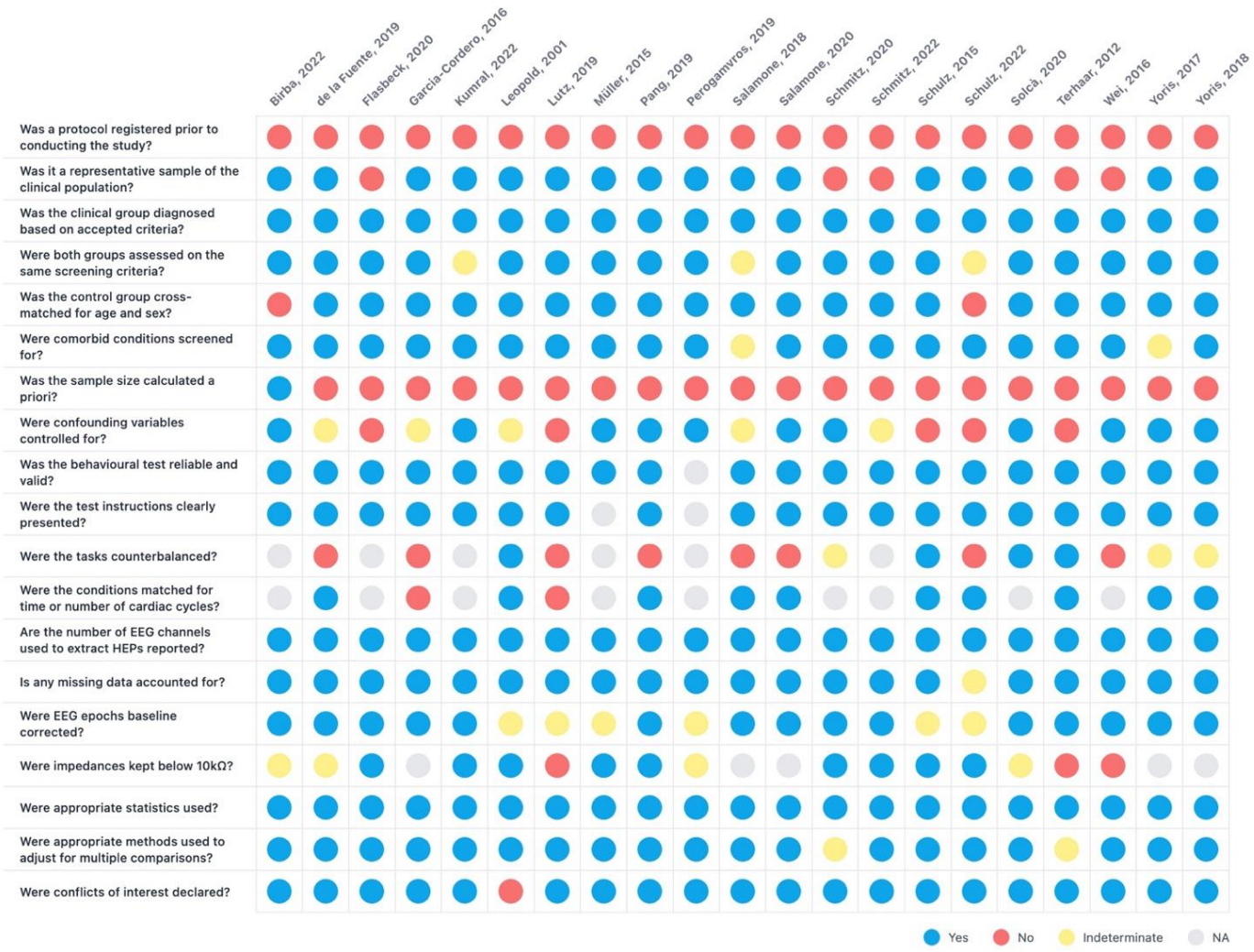
| Author (year) of included study | Diagnostic condition | N (F, *m* age ± SD) | HEP measured condition (mins) | Reported HEP outcome in clinical group compared to control |
|---|---|---|---|---|
| Birba et al. (2022) ^ | Fronto-temporal dementia (bvFTD)<br>Alzheimer's disease (AD) | Clinical: bvFTD 19 (5, *68.57* ± 1.92)<br>Clinical: AD 33 (20, *74.65* ± 1.55)<br>Healthy: 42 (23, *69.87* ± 1.5) | EC rs (10 min) | Larger HEP FTD (*d* = 0.78)<br>Smaller HEP AD (*d* = -1.77) |
| de la Fuente et al. (2019) | Smoked cocaine dependence | Clinical: 25 (2, *20.04* ± 2.28)<br>Healthy: 25 (3, *19.60* ± 2.62) | HTT | Larger HEP (*d* = 0.87)* |
| Flasbeck et al. (2020) | Borderline personality disorder | Clinical: 20 (17, *31.2* ± 10.4)<br>Healthy: 20 (17, *27.4* ± 5.8) | EC rs (8 min) | Smaller HEP (*d* = -0.39) |
| Garcia-Cordero et al. (2016) ^ | Behavioural variant frontotemporal dementia (bvFTD)<br>Alzheimer's disease (AD)<br>Fronto-insular stroke (FIS) | Clinical: bvFTD 9 (5, *63.67* ± 13.56)<br>Clinical: AD 9 (8, *72.33* ± 9.95)<br>Clinical: FIS 9 (3, *65.88* ± 9.12)<br>Healthy: 22 (12, *64.68* ± 5.98) | HTT | Smaller HEP in all clinical groups<br>(bvFTD *d* = -1.52, AD *d* = -1.77, FIS *d* = -2.19) |
| Kumral et al. (2022) | Atrial fibrillation | Clinical: 56 (12, *72.02* ± 4.15)<br>Healthy: 56 (12, *71.73* ± 4.26) | EO rs (20 min) | Smaller HEP (*d* = -0.84) |
| Leopold et al. (2001) | Diabetic neuropathy | Clinical: 25 (14, *34*)<br>Healthy: 25 (NR) | HCT | Smaller HEP (*p* = 0.001)* |
| Lutz et al. (2019) | Anorexia nervosa | Clinical: 19 (19, *25.20* ± 5.28)<br>Healthy: 19 (19, *24.60* ± 3.94) | HCT | Larger HEP (*d* = 1.27) |
| Müller et al. (2015) | Borderline Personality Disorder | Clinical; 34 (24, *27.7* ± 6.8)<br>Healthy: 31 (16, *27.9* ± 6.7) | EC rs (5 min) | Smaller HEP (*p* = 0.001)* |
| Pang et al. (2019) | Generalised anxiety disorder | Clinical: 25 (16, *39.76* ± 11.08)<br>Healthy: 15 (12, *39.93* ± 8.94) | EC rs (3 min) | Larger HEP (*p* = 0.43) |
| Perogamvros et al. (2019) ^ | Nightmare disorder | Clinical: 11 (8, *35* ± 9.3)<br>Healthy: 11 (8, 33 ± 9.2) | REM and nREM sleep stages | Larger HEP in REM (*g* = 1.42)* and nREM (*g* = 0.26) |
| Salamone et al. (2018) | Multiple Sclerosis | Clinical: 34 (28, *38.58* ± 10.03)<br>Healthy: 46 (37, *37.48* ± 12.46) | HTT | Smaller HEP (*d* = -0.6) |
| Salamone et al. (2020) ^ | Heart transplant recipients (4- & 12-months post-transplant) | Clinical: 4mo 8 (3, *47.81* ± 14.49)<br>Clinical: 12mo 9 (4, *45.92* ± 15.93)<br>Healthy: 31 (11, *40.45* ± 18.2) | HTT | Smaller HEP at 4mo (*d* = -1.42) post-transplant Smaller HEP at 12mo (*d* = -1.16) post-transplant |

| | | | | |
|---|---|---|---|---|
| Schmitz et al. (2020) | Borderline Personality Disorder | Clinical: 53 (53, *27.8* ± 7.4)<br>Healthy: 60 (60, *27.8* ± 7.1) | Combined EC-EO rs (2 min each) | Smaller HEP (*g* = -0.31) |
| Schmitz et al. (2021) | Post-Traumatic Stress Disorder | Clinical: 24 (23, *36.21* ± 11.09)<br>Healthy: 31 (29, *31.06* ± 9.19) | EC rs (5 min) | Larger HEP (*d* = 0.2) |
| Schulz et al. (2015) | Depersonalisation/ derealisation disorder | Clinical: 23 (12, *26.8* ± 6.5)<br>Healthy: 24 (13, *26.4* ± 2.0) | Combined EO-EC rs (150 sec each); HCT | Smaller HEP during HCT (*d* = -0.19), larger during rs (*d* = 0.22) |
| Schulz et al. (2022) ^ | Major depressive disorder (MDD)<br>Somatoform disorder | Clinical: MDD 24 (12, *40.9* ± 10.8)<br>Clinical: Somatoform 24 (20, *37.2*, ± 13.7)<br>Healthy: 22 (14, *31.1* ± 11.2) | HCT | Smaller HEP (MDD *g* = -0.34, SD *g* = -0.48) |
| Solcà et al. (2020) | Complex Regional Pain Syndrome | Clinical: 12 (7, *53.3* ± 12)<br>Healthy: 18 (7, *50.6* ± 11) | EO rs (5 min) | Smaller HEP (*g* = -2.25) |
| Terhaar et al. (2012) | Major depressive disorder | Clinical: 16 (13, *41.75* ± 12.4)<br>Healthy: 16 (12, *39.81* ± 17.6) | HCT | Smaller HEP (*p* = 0.017) * |
| Wei et al. (2016) | Insomnia | Clinical: 32 (25, *48.5* ± 14.1)<br>Healthy: 32 (26, *46.8* ± 15) | EC rs (5 min) | Larger HEP (*g* = 0.76) |
| Yoris et al. (2017) ^ | Obsessive compulsive disorder (OCD)<br>Panic disorder | Clinical: OCD 15 (8, *30.40* ± 9.98)<br>Clinical: Panic 15 (9, *35.46* ± 8.99)<br>Healthy: 25 (14, *33.45* ± 11.55) | HTT | Larger HEP in OCD (*g* = 1.86) *<br>Smaller HEP in panic (*g* = -0.5) |
| Yoris et al. (2018) | Hypertension | Clinical: 24 (12, *67.86* ± 9.09)<br>Healthy: 26 (17, *65.92* ± 7.51) | HTT | Smaller HEP (*d* = -0.37) * |

**Legend:** *d*: Cohen's d effect estimate; EC: eyes-closed resting state; EO: eye-open resting state; F: female; HCT: heartbeat counting task; HTT: heartbeat tracking task; mo: months; n: sample number; nREM: non-rapid eye movement; REM: rapid eye movement; rs: resting state; SD: standard deviation
* denotes significant effect estimate; ^ denotes multiple effects

## Risk of Bias of included studies

Overall, the included studies were deemed to have a low risk of bias (see *Figure 2*). Bias was highest in three criteria: protocol registration; sample size calculation; and impedance levels. Five studies used a predominantly or completely female cohort even though the condition does not predominantly or completely affect females (Flasbeck et al., 2020; Park & Blanke, 2019; Schmitz et al., 2020; Terhaar, Viola, Bär, et al., 2012; Y. Wei et al., 2016). Seven studies did not counterbalance tasks (de la Fuente et al., 2019; Flasbeck et al., 2020; Garcia-Cordero et al., 2016; Lutz et al., 2019; Pang et al., 2019; Salamone et al., 2018, 2020; Y. Wei et al., 2016); three studies did not report whether or not they counterbalanced tasks (Schmitz et al., 2020; Yoris et al., 2017, 2018). Three studies did not maintain an impedance level below the recommended 10kΩ (Lutz et al., 2019; Terhaar, Viola, Bär, et al., 2012; Y. Wei et al., 2016); four studies did not report whether impendences were kept below 10kΩ (Birba et al., 2022; de la Fuente et al., 2019; Perogamvros et al., 2019; Solcà et al., 2020); four studies used an active EEG system which does not require such low impedances and were therefore listed as *NA* for this criterion (Garcia-Cordero et al., 2016; Salamone et al., 2018, 2020; Yoris et al., 2017, 2018). Five studies did not report whether they controlled for confounding variables, such as medication or comorbid conditions (de la Fuente et al., 2019; Garcia-Cordero et al., 2016; Leopold & Schandry, 2001; Salamone et al., 2018). Given these diagnostic conditions include neurodegenerative conditions, substance use disorder, diabetic neuropathy, post-traumatic stress disorder, and hypertension, it is possible that participants in these clinical groups were medicated or actively taking a dependent substance. Four studies reported medication use but do not control for this in their analysis (Flasbeck et al., 2020; Lutz et al., 2019; Terhaar, Viola, Bär, et al., 2012; Yoris et al., 2017).




## Figure 2. Risk of Bias of Included Studies

**Legend:** Blue dots represent ‘yes’, red dots represent ‘no’, yellow dots represent ‘indeterminate’, and grey represents ‘NA’ for not applicable.

**Table 3. Meta-Analysis Appraisal Questions**

| # | Appraisal Question | Evidence | Page |
|---|---|---|---|
| 1 | Is the search systematic and transparently documented? | Date of search and databases are documented. Keyword strings and inclusion criteria documented. | 3 |
| 2 | What question and what effect size? | Research question documented. Required effect size documented. | 3, 5 |
| 3 | Is non-independence considered? | Yes. Non-independence is considered where multiple data points were listed from the same study, by running a multilevel meta-analytical model. | 5 |
| 4 | Which meta-analytic model? | A multilevel meta-analytic model was conducted to account for non-independence as 6 included studies reported multiple effect sizes. | 5 |
| 5 | Is the level of consistency among studies reported? | Yes. | 8 |
| 6 | Are the causes of variation among studies investigated? | Multiple lines of potential variation are investigated in the subgroup and moderator analyses and discussed in terms of overall heterogeneity in the discussion. | 14-15 |
| 7 | Are effects interpreted in terms of biological importance? | The effects are presented as effect estimates to describe the magnitude of difference between individuals with a clinical condition and a healthy comparison group. | 13-15 |
| 8 | Has publication bias been considered? | A funnel plot was drawn, demonstrating effect size and standard error/inverse of standard error to assess for small-study bias, and the asymmetry was discussed. A sensitivity analysis of small-study bias was fitted in a uni-moderator meta-regression, confirming the previous findings. | 6, 10 |
| 9 | Are results robust and unbiased? | Following the meta-analysis appraisal questions set out by Nakagawa et al. (2017), the event-related potential and publication guidelines set out by Picton et al. (2000), as well as conducting a multilevel meta-analytic model, the research team is confident the results are robust and unbiased. | 8, 10, 13 |
| 10 | Is the current state (and lack) of knowledge summarised? | The current state of knowledge is presented in the introduction before being summarised with results of the current review in the discussion. | 2-3 |

## Evaluation of the meta-analytic process

The quality of this meta-analytic process was evaluated (see *Table 3*), following the ten appraisal guidelines set out by Nakagawa et al. (2017). All ten quality appraisal questions were satisfied, providing confidence that the findings of this review are robust and transparent.

## Exploratory analysis: Visual inspection of data

A visual inspection of the data (*Figure 3*), using standard error as the measure of study size, did not reveal any outliers in the dataset, but it does indicate funnel plot asymmetry and bias towards less powerful studies (Sterne & Egger, 2001).

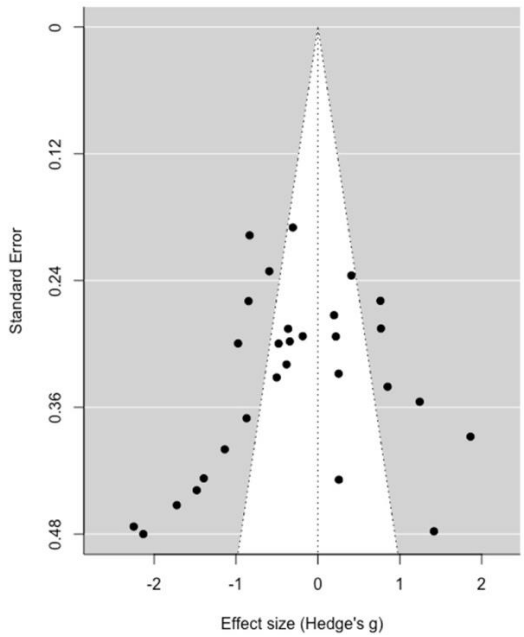



**Figure 3. Funnel plot of precision (standard error) for each outcome.**

**Note:** Each dot represents an outcome, the y axis represents study precision as quantified by SE of the effect of condition on HEP and the x axis shows the outcome effect size. In the absence of publication bias and heterogeneity there would be 95% confidence that the outcomes would fall within the white area of the cone.

**Table 4. EEG parameters and methodology**

| Author (year) of included study | Data Acquisition | Data Processing | Epoch (ms) relative to R-peak | Baseline correction (ms) | Artifact detection | Topography (number of electrodes) | Voltage measure | Latency investigated & reported (ms) | Statistical analysis & reported effect(s) | Control for Multiple Comparisons |
|---|---|---|---|---|---|---|---|---|---|---|
| **Birba et al. (2022)** | 128 electrodes (BioSemi), SR 1024Hz, ref linked mastoids, BP 0.03-100Hz | Ref CA, resampled 512Hz, filter 0.5-40Hz | -300 to 800 | -300 to 0 | EOG corrected for artifacts via ICA and visual inspection | Right centrotemporal (NR) | Point by point | 290-600 | Monte Carlo Permutation T-test; Cohen's d & p value | Monte Carlo Permutation T-test |
| **de la Fuente et al. (2019)** | 128 electrodes (BioSemi), SR 1024Hz, BP 0.5-30Hz | Ref mastoids, resampled 256Hz | -200 to 800 | -200 to 0 | Automated EEGLAB procedure | Frontal (9) | Point by point | 671-722 | Monte Carlo Permutation T-test; Cohen's d | Monte Carlo Permutation T-test |
| **Flasbeck et al. (2020)** | 32 passive electrodes, Impedance <5kΩ, SR 250Hz, BP 0.3-70Hz | Re-ref mastoids, 50Hz notch, filter 0.1-35, 24 dB/ octave roll-off Hz | -200 to 800 | -200 to 0 | EOG corrected + artifacts visual inspected | Frontal (7) | Mean amplitude | 252-620 | Mixed model ANOVA; Cohen's d | Bonferroni correction |
| **Garcia-Cordero et al. (2016)** | 128 electrodes (BioSemi), BP 0.5-30Hz, Ref CA | Resampled 256Hz | -200 to 400 | -200 to 0 | CFA + EOG contamination removed via visual inspection + ICA | Frontal-right (4), Frontal-central (4), Frontal-left (4) | Point by point | bvFTD: 277-355<br>AD: 113-132, 261-300<br>FIS: 191-355 | Monte Carlo Permutation T-test; Cohen's d | Monte Carlo Permutation T-test |
| **Kumral et al. (2022)** | 34 electrodes, SR 1000Hz, Imp <10kΩ | Ref CA, re-sampled 500Hz, low-pass 29-80Hz,<br>filter 1-45Hz,<br>notch filter 50Hz | -100 to 600 | -200 to 0 | Semi-automatic pipeline for artifact rejection<br>ICA removed confounding artifacts | Right frontal-temporal channels (12) | Mean amplitude | 300-550 | Monte Carlo Permutation T-test; Cohen's d | Monte Carlo Permutation T-test |
| **Leopold et al. (2001)** | 18 electrodes (Electro Cap), Imp <5kΩ, ref averaged ear lobe | SR 200Hz, filter 0.016-70Hz | -50 to 530 | NR | EEG sweeps accompanied by an EOG signal over 50uV rejected | Frontal (7), Central (3), Parietal (3), Temporal (4) | Mean amplitude | 280-330 | MANOVA; p value | Bonferroni correction |
| **Lutz et al. (2019)** | 64 electrodes (Acti-CAP), Imp <40kΩ, SR | Ref mastoids, | -200 to 1000 | NR | Visual inspection and EOG artifacts | Whole (64) | Mean amplitude | 455-595 | ANOVA; Cohen's d | Bonferroni correction |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1000Hz, BP 0.1-35Hz, ref FCz | high-pass filter 0.016Hz | | | corrected with Gratton-Coles algorithm | | | | | |
| **Müller et al. (2015)** | 60 electrodes (EasyCap), Imp <10kΩ, SR 1000Hz, BP 0.1-35Hz, ref CA | Resampled 250Hz | -200 to 1000 | NR | EOG artifacts corrected for artifacts, + semi-automatic rejection of trials with artifacts | Fz, Cz, Pz, Oz | Mean amplitude | 455-595 | ANOVA; p value | Dunn multiple comparisons test |
| **Pang et al. (2019)** | 64 electrodes (BrainCap), Imp <10kΩ, BP 0.1-30Hz, SR 500Hz, ref nose | Low-pass filter 30 Hz | -200 to 800 | -200 to 0 | ECG and EOG artifacts visually inspected ICA | Frontal (6) | Mean amplitude | 240-460 | ANOVA; p value | Cluster-based permutation procedure |
| **Perogamvros et al. (2019)** | 20 electrodes (Deltamed), SR 512Hz, ref FPz | Ref CA, resampled 256Hz, filter 1-40 Hz | -300 to 700 | NR | Visual inspection + ICA | Frontal (4) | Mean amplitude | 449-504 | Monte Carlo Permutation T-test; p value | Monte Carlo Permutation T-test |
| **Salamone et al. (2018)** | 128 electrodes (Biosemi), Imp <40mV, SR 102EH4Hz | Ref mastoids, resampled 256Hz, filter 0.5-30Hz | -200 to 500 | -200 to 0 | CFA + EOG artifacts removed through ICA and visual inspection | Frontal (6) | Point by point | 200-500 | Monte Carlo Permutation T-test; Cohen's d | Monte Carlo Permutation T-test |
| **Salamone et al. (2020)** | 128 electrodes (Biosemi), SR 1024Hz | Ref CA, resampled 256Hz, filter 0.5-30Hz | -300 to 600 | -300 to 0 | EOG artifacts corrected with ICA + visual inspection | Central (20) | Point by point | 200-500 | Monte Carlo Permutation T-test; Cohen's d | Monte Carlo Permutation T-test |
| **Schmitz et al. (2020)** | 60 electrodes (EasyCap), Imp < 10kΩ, SR 1000Hz, BP 0.01-200Hz, Ref CA | Resampled 250Hz, filter 0.1-35Hz | -200 to 1000 | -200 to 0 | EOG artifacts via Gratton-Coles algorithm, semi-automatic artifact rejection | Whole (60) | Mean amplitude | 455-595 | rmANCOVA; m (SD) | NR |
| **Schmitz et al. (2021)** | 60 electrodes (EasyCap), Imp < 10kΩ, SR 1000Hz, BP 0.01-200Hz, ref CA | Resampled 250Hz, filter 0.1-35Hz, 24 dB/octave | -200 to 1000 | -200 to 0 | EOG artifacts corrected, semi-automatic artifact rejection | Whole (60) | Mean amplitude | 455-595 | T-test; Cohen's d | Bonferroni correction |
| **Schulz et al. (2015)** | 2 electrodes (Biopac), Imp <10kΩ, high-pass | Resampled 256Hz, filter 0.1-35Hz, 24 | -200 to 1000 | NR | Visual inspection, artifacts excluded EOG correction via | Central (2) | Mean amplitude | 455-595 | T-test; m (SD) | Bonferroni correction |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | filter 0.1Hz, digitised 1kHz, ref NR | dB/octave | | | Gratton-Coles algorithm | | | | | |
| **Schulz et al. (2022)** | 64 electrodes (BrainAmp), Imp < 10kΩ, digitised 1kHz, BP 0.0159-250Hz (24db), Ref FCz | Ref mastoids, re-sampled 256Hz, re-filter 0.1-35Hz | -200 to 1000 | NR | Visual inspection, excluded EOG correction via Gratton-Coles algorithm | Whole (64) | Mean amplitude | 455-595 | ANOVA; m (SD) | Greenhouse-Geisser |
| **Solcà et al. (2020)** | 64 electrodes (Biosemi), Imp < 20kΩ, SR 2048Hz, low-pass filter 400Hz | Ref average, resampled 512Hz, filter 1-40Hz | -200 to 600 | -200 to 0 | EOG, CFA, saccades, noise corrected via ICA | Central (6) | Mean amplitude | 200-330 | Monte Carlo Permutation T-test; m (SD) | Monte Carlo Permutation T-test |
| **Terhaar et al. (2012)** | 63 electrodes (EasyCap), Imp < 20kΩ, SR 500Hz, high pass 0.1Hz, ref Cz | Ref CA, resampled 256Hz, filter 1-40Hz, | -200 to 800 | -200 to 0 | EEGLAB joint probability measure, ICA EEGLAB plugin CORRMAP for EOG + CFA | Whole (62) | Mean amplitude | 128-264, 356-456, 536-592 | ANOVA; p value | Greenhouse-Geisser |
| **Wei et al. (2016)** | 256 electrodes (HydroCel), Imp < 100kΩ, BP 0.1-100Hz, ref Cz | Digitised 1000Hz, down sampled 250Hz, filter 0.5-62.5Hz | -300 to 600 | -300 to -100 | ICA, visual inspection | Whole (150) | Mean amplitude | 200-600 | Monte Carlo Permutation T-test; m (SD) | Monte Carlo Permutation T-test |
| **Yoris et al. (2017)** | 128 electrodes (BioSemi), SR 1024Hz, ref mastoids | Ref CA, resampled 256Hz | -200 to 500 | -200 to 0 | EOG + cardiac artifacts removed using ICA and visual inspection | Right-prefrontal (4) | Mean amplitude | OCD: 190 Panic: 182 | Monte Carlo Permutation T-test; p value | Monte Carlo Permutation T-test |
| **Yoris et al. (2018)** | 128 electrodes (BioSemi), ref mastoids | Ref CA, resampled 256Hz | -200 to 500 | -200 to 0 | EOG + cardiac artifacts removed via ICA and visual inspection | Frontal (10) | Point by point | 200-500 | Monte Carlo Permutation T-test; Cohen's d | Monte Carlo Permutation T-test |

**Legend:** AD: Alzheimer's disease; ANOVA: Analysis of variance; BP: Bandpass filter; bvFTD: Behavioural variant frontotemporal dementia; CA: Common average; CFA: Cardiac field artifact; EEG: Electroencephalography; EEGLAB: MATLAB EEG analysis toolbox; EOG: Electrooculography; FIS: Fronto-insular stroke; Hz: Hertz; ICA: Independent components analysis; Imp: Impedance; kΩ : Kiloohm; m; Mean; ms: Milliseconds; MANOVA: Multivariate analysis of variance; NR: Not reported; OCD: Obsessive compulsive disorder; Ref: Reference; rmANCOVA: Repeated measures analysis of covariance; SD: Standard deviation; SR: Sampling rate

## Overall effect estimate

A total of 29 effects were included in the random effects multi-level meta-analysis from the 21 included studies. The estimated average standardised mean difference based on the random-effects model was -0.256 (95% CI: -0.666 to 0.154). A 95% prediction interval for the true outcome is given by -2.153 to 1.641, indicating that in some studies, the true outcome may be positive. The small negative effect estimate (Cohen, 1992) demonstrates an overall reduced HEP amplitude in clinical groups relative to healthy controls, but this overall effect was not significant ($t(20) = -1.302$, $p = 0.208$). A forest plot of the observed outcomes and the estimate based on the random-effects multilevel model is shown in *Figure 4*.

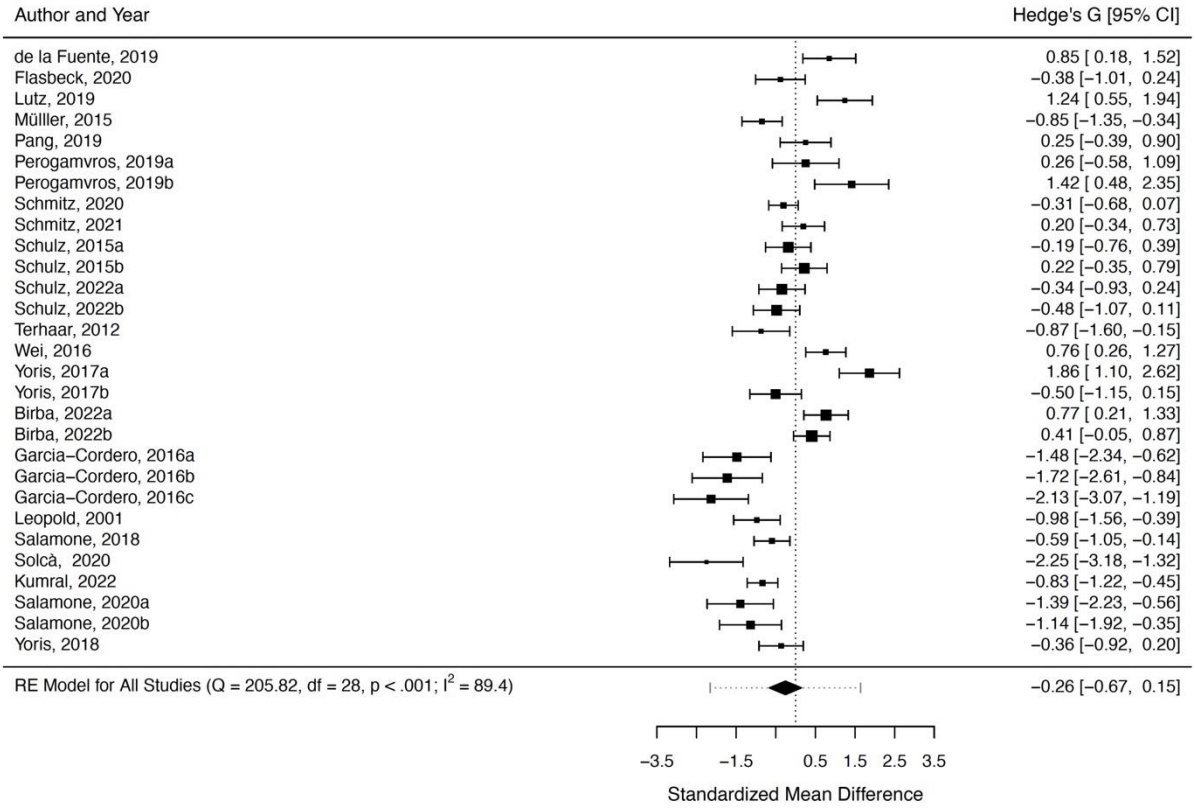



**Figure 4. Forest plot of the observed outcomes and the estimate of the random-effects multilevel meta-analytic model**

**Note:** The overall prediction interval is denoted by horizontal dashed lines either side of the overall pooled estimate.

## Level of variance within the random effects multilevel model

The level of variance that contributed to each level of the model was estimated using a log-likelihood-ratio test (see *Table 5)*. When the full model was compared to a reduced model without within-study variance, the within-study variance was significant ($p$ = 0.002), demonstrating significant variability between effect sizes within studies. When the full model was compared to a reduced model without between-study variance, the between-study variance was also significant ($p$ = 0.015) when divided by two to account for the one-sided log-likelihood-ratio tests (Assink & Wibbelink, 2016). Therefore, the fit of the original multilevel model is statistically better than the fit of either of the two reduced models (evidenced by smaller AIC and BIC), indicating significant variability both between effect sizes within studies (Level 2) and between all studies (Level 3). The total variance across the three levels of the model (89.4%) estimated that within-study sampling (Level 1) explained 10.6% of the total variance, within-study effect size (Level 2) explained 31.8% of the total variance, and for between study variance (Level 3) explained 57.7% of the total variance. The typical within-study sampling variance at Level 1 was less than 75% of the total amount of variance, demonstrating substantial variation at Level 2 and Level 3. Consequently, a moderator analysis was carried out (Hunter & Schmidt, 2004).

**Table 5. Multilevel model results**

| n | k | Meta-analytic mean | 95% CI | 95% PI | $I^2$ residual (%) | $I^2$ study (%) | $I^2$ total (%) |
|---|---|---|---|---|---|---|---|
| 21 | 29 | -0.256 | [-0.666, 0.154] | [-2.153, 1.641] | 31.766 | 57.667 | 89.434 |

**Note:** N: Number of studies; k: Number of effects; CI: Confidence interval; PI: Prediction interval; I2: Heterogeneity

## Subgroup analysis: Diagnostic Group

During data extraction, the included studies were identified as fitting into one of three clinical categories: psychiatric, neurological, and cardiovascular. This categorisation was confirmed using standard diagnostic classification guidelines (DSM, ICD). This led to the decision to perform a subgroup analysis of each diagnostic group to determine the average effect in each group. The findings of the subgroup analyses are illustrated in the forest plot in *Figures 5* to *7*.

## Psychiatric Conditions

A small positive effect estimate (Hedge's *g* = 0.049, *SE* = 0.073, 95% CI = -0.095 to 0.192) was found in the psychiatric subgroup analysis (see *Figure 5*), indicating no difference in HEP amplitude in individuals with a psychiatric condition when compared to healthy comparisons.




### Figure 5. Subgroup analysis of psychiatric conditions

**Note:** The estimates to the left of 0 indicate lower HEP amplitude in the clinical group compared to their healthy comparison group. The estimates to the right of 0 indicate high HEP amplitude in the clinical group compared to their healthy comparison group. The size of the square in the centre of each effect estimate is proportional to the weight of the study in relation to the pooled estimate. Additional variables (task condition, time window, and topography) have been illustrated to demonstrate the variability in methodological decisions. The time window panel illustrates both the time window investigated (light blue) and the time window that HEP was reported (dark blue). See Table 4 for a list of the studies that contributed more than one effect size.

## Neurological Conditions

A medium negative effect estimate (Hedge's *g* = -0.513, 95% CI = -0.733 to -0.293, *SE* = 0.112, *p* = 0.0001) was found in the neurological subgroup analysis (see *Figure 6*), indicating a significantly lower HEP amplitude in individuals with a neurological condition when compared to healthy comparisons.

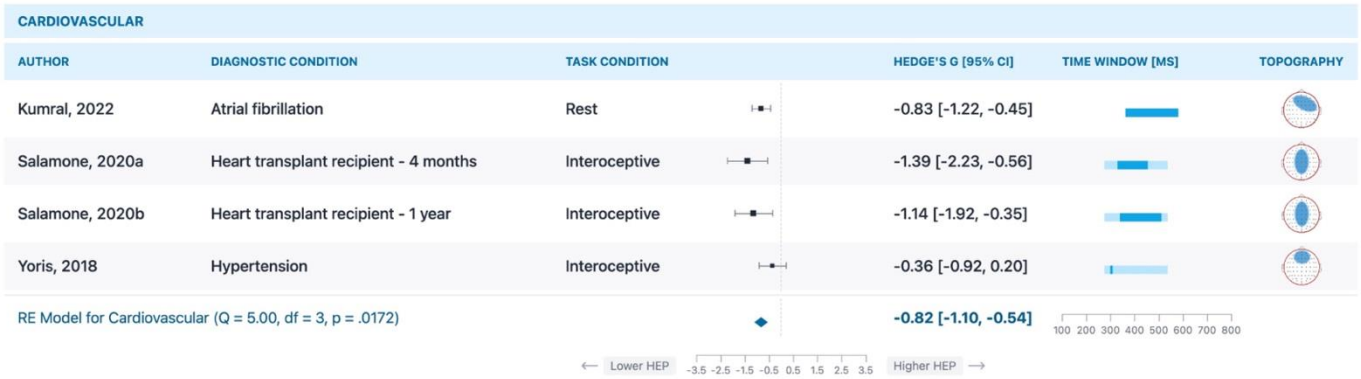



**Figure 6. Subgroup analysis of neurological conditions**

**Note:** The estimates to the left of 0 indicate lower HEP amplitude in the clinical group compared to their healthy comparison group. The estimates to the right of 0 indicate high HEP amplitude in the clinical group compared to their healthy comparison group. The size of the square in the centre of each effect estimate is proportional to the weight of the study in relation to the pooled estimate. Additional variables (task condition, time window, and topography) have been illustrated to demonstrate the variability in methodological decisions. The time window panel illustrates both the time window investigated (light blue) and the time window that HEP was reported (dark blue). See Table 4 for a list of the studies that contributed more than one effect size.

## Cardiovascular Conditions

A large negative effect estimate (Hedge's *g* = -0.818, *SE* = 0.142, 95% CI = -1.096 to -0.541) was found in the cardiovascular subgroup analysis (see *Figure 7*), indicating a significantly lower HEP amplitude in individuals with a cardiovascular condition when compared to




healthy comparisons.

**Figure 7. Subgroup analysis of cardiovascular conditions**

**Note:** The estimates to the left of 0 indicate lower HEP amplitude in the clinical group compared to their healthy comparison group. The estimates to the right of 0 indicate high HEP amplitude in the clinical group compared to their healthy comparison group. The size of the square in the centre of each effect estimate is proportional to the weight of the study in relation to the pooled estimate. Additional variables (task condition, time window, and topography) have been illustrated to demonstrate the variability in methodological decisions. The time window panel illustrates both the time window investigated (light blue) and the time window that HEP was reported (dark blue). See Table 4 for a list of the studies that contributed more than one effect size.

## Moderator analysis: Task Condition

The regression coefficient of the variable 'task' does not differ significantly from zero, therefore we can conclude that the overall effect estimate (-0.256) is not moderated by the task condition (i.e., interoceptive or resting state recording) of the included studies ($F(1, 27) = 0.817$, $p = 0.38$).

## Sensitivity analysis: Uni-moderator analysis to assess for small-study effects

To test for publication bias, a uni-moderator meta-regression was fitted to assess for small-study effects in the data set after accounting for non-independence. Effect size standard error (SE) was included as the only moderator. The results indicate the existence of small-study effects since the slope of the moderator SE is statistically significant (slope = -1.418, 95% CI = -6.378 to 3.543, $R^2_{marginal}$ = 19.8%). These results support the findings from the funnel plot (*Figure 3*) and indicate that we need to be circumspect in our interpretation of the findings of this review.

## Discussion

The primary aim of this quantitative meta-analytic review was to determine whether, and to what extent, the amplitude of the heartbeat evoked potential differs between clinically diagnosed subgroups and healthy comparisons. We found evidence to suggest that the relationship between interoception and clinical pathology varies depending on the type of condition; that is, while some conditions showed a reduced HEP amplitude, others showed an increased one. Overall, we did not find evidence to support a directional relationship between HEP and all clinical conditions evaluated. We found evidence to support a consistent directional relationship between HEP amplitude in neurological and cardiac conditions, where HEP amplitude was significantly lower in the clinical group than it was in the healthy comparison group. We did not find evidence to support a directional relationship between HEP and psychiatric conditions. The second aim of this review was to systematically characterise the methodological parameters used to record and analyse HEP to date in the literature. However, we found many methodological inconsistencies between studies at all points in the collection of HEP data, limiting the potential inferences that can be drawn. Although such large heterogeneity could be explained by the clinical nature of this review, below we discuss the potential role of the methodological inconsistencies in the context of the meta-analytical findings.

### Aim 1. Subgroup Analysis: Diagnostic Condition

#### Psychiatric Conditions

While the psychiatric group (17 effects across 13 studies) showed no difference in interoceptive response to the healthy group, many studies reported comorbid conditions, such as anxiety and depression (as we demonstrate in *Figure 2*). Unaccounted-for variables such as comorbidities, or associated characteristics including medication, and diagnostic severity, are thus possible confounders in the effect. For example, Terhaar et al. (2012) reported HEP in a depressive cohort with mixed diagnostic severity (varying in number of episodes and ranging from mild to severe) but did not control for severity. Further, Yoris et al. (2017), who examined HEP in obsessive compulsive disorder and panic disorder, reported mild to moderate depression in both clinical groups, but did not control for depression in their analysis. As we were limited to the author reports about the diagnosis of the condition, we cannot improve precision of the diagnosis or classify across the studies by the dimensions of the presenting condition. Given the clinical and largely exploratory nature of this review, this is likely a difficult element to control. Future studies investigating HEP in

clinical cohorts could likely benefit from accounting for extraneous variables such as comorbidities, diagnostic severity, and medication usage.

One approach may be to mechanistically perturb the interoceptive system via top-down or bottom-up probes. Verdonk et al. (2024) used such an approach in generalised anxiety disorder and compared the administration of a peripheral adrenergic modulator in patients with generalised anxiety disorder to healthy comparisons. They observed abnormal changes in HEPs between groups, in both systole and diastole windows (bottom-up evidence). Additionally, group differences at physiological rest (top-down evidence) were reported. Thus, this study illustrates how an approach that can disrupt the normal functioning of the interoceptive system may allow for a richer understanding of the underlying mechanisms and potential dysregulation in interoceptive processing in psychiatric conditions such as anxiety disorders. Additional studies of this type are needed to better understand the role of heartbeat-evoked neural signals in psychiatric disorders.

### Neurological Conditions

The neurological group (eight effects across five studies) showed a significantly lower HEP amplitude than the healthy group. That such a large group effect was found may reflect homeostatic dysregulation as has been demonstrated in neurological conditions included in our subgroup such as multiple sclerosis (e.g., bladder, cardiovascular, gastrointestinal, and fatigue; Sirbu et al., 2020), complex regional pain syndrome (e.g., small nerve fibre degeneration; Marinus et al., 2011), diabetic neuropathy (e.g., autoimmune destruction of nerves; Vinik et al., 2003), and neurodegenerative diseases (Femminella et al., 2014). Additionally, there is evidence to suggest that abnormal cardiovascular functioning is prevalent in some neurological conditions, such as orthostatic hypotension in subsets of dementia, and cardiovascular autonomic dysfunction is evident in as many as 42% of people living with multiple sclerosis (Christiansen et al., 2010; Kaplan et al., 2015). Thus, there could be heterogenous contributions to HEP within neurological subgroups.

It seems possible that age related effects may contribute to the reduced HEP in the neurological subgroup (mean age per subgroup: psychiatric 31.8, neurological 52.3, cardiovascular 61.2 years), a possibility which is concordant with studies demonstrating reduced interoceptive awareness in older adulthood (Khalsa, Rudrauf, & Tranel, 2009; Murphy et al., 2018). Conversely, Kamp et al. (2021) found that older adults exhibited an increased HEP amplitude compared to young adults in the absence of major health

concerns or disorders. However, the study did not examine group differences in arterial wall stiffness or cardiac contractility despite including heart rate and heart rate variability as covariates in some analyses. If it were the case that although both groups had equal cardiac output, the older participants had stiffer vessel walls – consistent with aging physiology – this may translate to a greater mechanosensory reverberation during systole. Such an explanation might plausibly account for the effects observed within 180 to 320 ms after R-wave onset in the 'early control window.'

### Cardiovascular Conditions

The cardiovascular group (four effects over three studies) showed a significantly lower HEP amplitude than the healthy group. This reduced HEP amplitude may reflect the fact that HEP is thought to measure cardiac interoception via baroreceptors at the aortic arch and carotid arteries, and so abnormal cardiovascular function, like hypertension (Yoris et al., 2018) and arterial fibrillation (Kumral et al., 2022), may alter the HEP response by altering the behaviour of these receptors (Park & Blanke, 2019). However, other pathways have been proposed that may reflect a combination of input from baroreceptors and dermal/subdermal mechanosensory receptors on the perception of cardiac signals (Cameron & Minoshima, 2002; Khalsa, Rudrauf, Feinstein, et al., 2009; Knapp-Kline et al., 2021; Park & Blanke, 2019).

Additionally, the vagal denervation occurring as a result of the heart transplant procedure provides a unique opportunity to glean insights to the peripheral pathways contributing to heart-brain communication (Barsky et al., 1998; Salamone et al., 2020). Beyond the pathophysiological changes occurring in the cardiovascular system, Mauthner et al. (2015) highlight that post-heart transplant patients report experiencing emotional difficulties such as distress and detachment from their bodies; such aspects are clearly interrelated with one's interoceptive sense of self, and as such, may influence HEP (Schulz, Koster, et al., 2015; Terhaar, Viola, Bär, et al., 2012).

## Aim 2. Methodological Parameters

### Active and passive recordings of HEP

The concept of interoception and what constitutes an interoceptive task remains a contentious topic in the field (Ainley et al., 2020; Brener & Ring, 2016; Corneille et al., 2020;

Legrand et al., 2021; Zamariola et al., 2018; Zimprich et al., 2020). As such, it was decided *a priori* that any HEP assessment that the authors stated as interoceptive – either active or passive – would be included in the meta-analysis. As such, both active and passive interoception assessments were represented in the studies included in this review. Active interoception assessments included accuracy tasks that draw explicit attention to the heartbeat. Passive assessments included resting state EEG recordings, which do not draw explicit attention to the heartbeat. Regardless of the approach, there was considerable variation in participant instruction and condition parameters. As it is suggested that HEP is enhanced during attention to interoceptive signals (Montoya et al., 1993; Petzschner et al., 2019; Pollatos & Schandry, 2004; Schandry & Montoya, 1996), we decided *post-hoc* to perform a moderator analysis to determine the influence of active or passive tasks on HEP amplitude. Contrary to our expectation, task did not significantly ($p$ = 0.74) moderate the overall effect estimate (g = -0.256). The lack of moderation effect may also be explained by the small sample size, methodological variation, and the influence of participant beliefs about their own heart rate (Brener & Ring, 2016; Desmedt et al., 2018; Legrand et al., 2021; Ring et al., 2015).

Two active interoceptive accuracy tasks were used to measure a HEP response: heartbeat tapping task (HTT) and heartbeat counting task (HCT). The HTT involves keyboard tapping to endorse each felt heartbeat and requires both attention to the heartbeat and effective performance of the motor response. However, concerns have been raised about how this dual task might interfere with perception of heartbeats (Pennebaker & Hoover, 1984) and confound results physiologically with competing motor-evoked potentials (Brener & Ring, 2016; Flynn & Clemens, 1988). Similarly, in the HCT, participants are required to keep track of the heartbeats they feel for a given time which risks capturing more than just interoceptive activity, as participants switch back-and-forth between detecting each beat and keeping count mentally. Taken together, these results suggest that studying heart-beat evoked responses during interoceptive perturbation Verdonk et al. (2024) may provide richer data and clearer HEP outcomes.

There is evidence supporting the argument that interoception is best captured in eyes-closed (EC) resting state EEG, and exteroception in eyes-open (EO) EEG (Marx et al., 2003; Pang et al., 2019; J. Wei et al., 2018; Y. Wei et al., 2016; Xu et al., 2014). However, for this study, we chose to take the author's opinion on what was considered an interoceptive task. As a result, some studies reported eyes-closed (EC) as interoceptive (Flasbeck et al., 2020;

Müller et al., 2015; Pang et al., 2019; Y. Wei et al., 2016), whereas others reported eyes-open (EO) as interoceptive (Kumral et al., 2022; Solcà et al., 2020), or an Interoceptive assessment based on the combined analysis EC and EO data (Schmitz et al., 2020; Schulz, Koster, et al., 2015). Wei et al. (2016) clearly identified different brain activations between EC and EO, confirmed by two spatiotemporal clusters. This potentially limits the interpretation of some of our findings where EO or a combined EO-EC is used as a method of recording HEP. We did not choose *a priori* to exclude EO tasks, because there was no clear consensus in the field. However, it seems possible that confining the assessment of HEP to EC conditions only may provide a less variable HEP signal. It may be helpful for future investigations of HEP if field-wide consensus was established on core assessments to be undertaken.

### Latency of HEP and other heart cycle-related artifacts

Across all effects, most (16 of 29) of the reported HEP outcomes were detected within the window of 300-600 ms post R-wave. The adherence to this time window is motivated by the proposal that there are minimal (<1% contamination) cardiac field artifacts (CFA) at 455-595 ms post r-wave (nearing the end of the T-wave and the start of the next P-wave; (Dirlich et al., 1997)). The CFA is considered a major methodological issue, as both the CFA and HEP are time-locked to the same event (Schandry et al., 1986) and so constraining HEP analysis to a largely CFA-free window is a common method to isolate HEP. However, other efficient approaches of removing heart cycle-related artifacts exist (e.g., principal component analysis and independent component analysis) that do not isolate the window of interest (Dirlich et al., 1998; Gray et al., 2007; Pollatos & Schandry, 2004; Terhaar, Viola, Bär, et al., 2012).

The remaining 13 studies employed mass-univariate analyses where they did not predetermine a window of interest. One common approach to defining the window of interest in HEP analysis is to use a permutation procedure (Groppe et al., 2011; Maris & Oostenveld, 2007; Todd et al., 2021). Such procedure runs thousands of random permutations of the data at every time point and electrode, and intrinsically accounts for the multiple comparison problem. This approach has clear benefits for the investigation of HEP in understudied clinical populations as it does not require time windows or regions of interest to be predetermined (Groppe et al., 2011; Verdonk et al., 2024). In this review, 15 of the 29 reported effects were determined via permutation testing, which based on the forementioned advantages, provides greater confidence in these 15 effects. Interestingly, all the included

neurological and cardiovascular studies employed Monte Carlo permutation testing, providing support for an optimal statistical analysis of HEP.

### Topography

The studies included in this review either extracted HEP from a frontotemporal region of interest, as is routine for healthy HEP topography (Babo-Rebelo et al., 2016; Gentsch et al., 2019; Montoya et al., 1993; Park & Blanke, 2019; Petzschner et al., 2019), or used a cluster-based analysis with input from all electrode sensors to assess HEP, of which a frontotemporal topography was still found. That a frontotemporal topography was consistently found independent of the method strengthens the robustness of an anatomical origin of HEP, but as these studies did not also employ a source localization approach, the precise neuroanatomical generators of the observed group differences in HEP amplitude remain unknown.

### Reference Electrode

HEP is susceptible to the same major methodological issues encountered when recording ERP signals; specifically, that the choice of reference site can have a substantial impact on the overall findings (Nunez, 1981; Hagemann, Naumann and Thayer, 2001; Zheng *et al.*, 2018; Candia-Rivera, Catrambone and Valenza, 2021; Soskic et al., 2022). Indeed, Candia-Rivera et al. (2021) acknowledged the susceptibility of HEP outcome to the reference selection, advocating for the common average as the optimal reference for HEP. This is further supported by Kern et al.'s (2013) recommendation that by re-referencing to the common average, the effects of the cardiac field artifact are minimised. While a mean mastoid reference selection may maximise effect size, referencing to a common average has the advantage of minimising noise (Šoškić, Jovanović, et al., 2022). Given the magnitude of the HEP signal, this parameter is worth consideration. The offline reference electrode used by studies included in the current review varied across conditions with the majority either being set to a common average or the mastoids. Other studies did not report the reference placement used, including Schulz et al. (2015), which contributed two effect sizes to the analysis. Taken together, it appears that adopting a common average reference may serve as the most optimal option for HEP analysis (Candia-Rivera et al., 2021; Kern et al., 2013). Nevertheless, Šoškić et al. (2022) demonstrate that consistency in referencing across studies can minimise variations in scalp voltage distribution and facilitate more accurate comparisons between studies.

## Impedance Levels

The HEP signal is very small (approximately 0.5-2uV; Dirlich et al., 1998; Schandry and Montoya, 1996) compared to the noise of both pulsatility (~5uV; Kern et al., 2013) and cardiac field artifacts (~17uV; Kern et al., 2013), meaning that reporting the impedance level that is accepted is necessary and should be standard practice. However, this review found inconsistencies in both the practice of maintaining minimal scalp-electrode impedance in EEG data collection (often below 10kΩ, indicating lower resistance to the current flow and improved signal to noise ratio) and reporting this decision in the manuscripts of the included studies. Some included studies did not report the level below which they kept their impedances, limiting their interpretation.

## Comparison to the literature

Our results are broadly consistent with those of Coll et al. (2021), who reported the effect of a clinical group on HEP as $g = 0.49$. Twelve studies were included in both reviews, and nine studies were more recent, and therefore only included in our review. We calculated larger effects of condition on HEP than Coll et al. in three studies (Lutz et al., 2019; Müller et al., 2015; Y. Wei et al., 2016). There are several important methodological differences that probably contribute to the different outcomes. Firstly, we contacted authors for raw data or exact effect estimates, whereas Coll et al. calculated the effect size as significant or non-significant "*assuming p= 0.05 or p = 0.5, respectively*" (Coll et al., 2021, p. 7) and calculated an effect estimated based on f-values. Secondly, Coll et al. averaged effect sizes prior to analysis if a study reported more than one statistic in the region of interest. We chose not to do this because averaging effect sizes in this way potentially leads to a loss of statistical power, unnecessarily large standard errors for the overall effect, and ultimately loses information as a result of not analysing within-study variance (Cheung, 2019; Nakagawa, Senior, et al., 2022). Thirdly, Coll et al. did not account for the interdependency of effect sizes even though three of their included studies contributed more than one effect size to the clinical HEP meta-analysis. We accounted for potential nonindependence when studies reported effects in multiple diagnostic conditions or task conditions, so we employed a multilevel meta-analytic model (Mengersen et al., 2013; Nakagawa & Santos, 2012; Noble et al., 2017). This difference in meta-analytic approach is perhaps an explanation for the variance in reported effect estimates, as Coll et al.'s approach may potentially have led to nested and less conservative effect estimates.

A methodological advantage implemented by Coll et al. (2021) is the mass-univariate analysis performed to assess the spatiotemporal distribution of effects. This allowed the authors to clearly identify the strongest temporal peak and region of interest, minimising heterogeneity of the data ($I^2 < 0.01$). Their results, indicating the strongest peak at 400 ms in right frontocentral electrodes is relatively consistent with the HEP literature (Gray et al., 2007; Kern et al., 2013) and supports the commonly used time window of 495-500 ms post R-wave to investigate HEP. This approach also came with limitations because it constrained the number of studies included in their analysis, limiting their overall clinical findings. Although Coll et al. did not pre-register their review, they provided full data and scripts on the open access repository, *Open Science Framework* – a clear commitment to transparent practice, and one that allowed our team to fully evaluate the sources of different results.

## Risk of Bias

The methods used to design and record HEP data show rigour in the field, but also reveal two things: the HEP signal contains a great deal of variability, and a clear interpretation of the relationship between the HEP signal and interoception is yet to be determined, particularly with respect to psychiatric conditions. The largest bias observed in the current review involved relatively recent standards. For example, pre-registration of study protocol, now recommended in many fields (see Lee et al., 2018), and fundamental considerations such as *a priori* sample size calculation. The risks to validity and transparency that such oversights bring can be easily eliminated moving forward, particularly if more journals move towards requiring them at manuscript submission stage. While these are recent practices, their implementation in the HEP field will improve confidence in the results of subsequent studies.

## Strengths and limitations of this review

We made every attempt to obtain missing data through correspondence with authors, but not all data could be accounted for. That some data could not be retrieved during the data extraction phase of this review mostly impacts our secondary aim of identifying the optimal parameters to use when analysing HEP amplitude in a clinical population. While compelling evidence suggests that the high heterogeneity in the meta-analysis is due to the wide range of clinical conditions investigated, it is likely that methodological decisions are also contributing factors. *Table 5* demonstrates the variety of methods taken in data collection, acquisition, and analysis. There is large variability in the decisions made by authors in terms of both the time window investigated and consequently reported on, and the reference

electrode chosen (both online and offline). These statistical decisions and their variability are illustrated in *Figures 5* to *7.* Overall, the high statistical heterogeneity, likely from a combination of clinical, methodological, and by-chance heterogeneity, limits the potential clinical inferences that may be drawn. This underscores the need for consensus-derived recommendations on core assessment tasks, HEP parameter selection and analysis approaches. It also points to the potential importance of further exploration of HEP in specific clinical populations, within the confines of such consensus recommendations.

## Suggestions for future research

To improve understanding of the stability of interoception across the lifespan, longitudinal data investigating implicit interoception, such as HEP, would be useful. As almost all studies included in this review were cross-sectional in nature, no evidence of a temporal relationship between interoception and diagnostic condition was possible, and as such, it is unwise to draw any causal inferences. However, early evidence that perturbations of heartbeat signals can identify abnormal HEPs in generalised anxiety disorder (Verdonk et al., 2024) raises the possibility that, with additional studies, the meta-analytic evidence based for HEP abnormalities in psychiatric disorders will be robust enough to make a final determination with regard to the nature of this signal.

In response to the call by Coll et al. (2021) for future research to consider the direction and amplitude of HEP to compare between clinical conditions, we made an *a priori* decision to examine both the direction of HEP and its amplitude, as reported in each paper. As mentioned by Coll et al., the direction of HEP is influenced by multiple pre-processing choices and interpretations which could not be accounted for in our analysis. As such, we endorse Coll et al.'s recommendation to consider a consensus on the assessment of HEP. In support of this, Šoškić et al. (2022b) report large effects of minor procedural deviations such as determining a low-pass filter, reference electrode, and measurement window, on the N400, known to be a large and robust ERP component. This means that smaller components, such as HEP, are more susceptible to such deviations. One suggestion to improve methodological consistency to guard against procedural deviations is to adopt the recently proposed ARTEM-IS (Agreed Reporting Template for EEG Methodology; Styles et al., 2021) checklist to standardise protocols, promote transparent reporting of methods and provide sufficient information for replication.

## Final remarks

HEP shows promise as a biomarker of interoception and there is a building body of literature on HEP in people with clinical conditions. The currently available evidence suggests that the amplitude of HEP is systematically reduced in people with neurological or cardiovascular conditions, but the same conclusion cannot be applied to people with psychiatric conditions. Methodological inconsistencies and shortcomings raise significant questions however, over the extent and nature of HEP disruption in clinical groups and in healthy participants, particularly with respect to psychiatric disorders. Accordingly, there is a pressing need for a field-wide consensus on the procedures, analyses, and reporting of HEP studies in humans to allow for comparison and pooling of data between studies and populations.

## Author Contributions

**Conceptualisation**: EMW, MK, GLM, CB. **Methodology**: EMW, HGJ, MK, GLM, CB. **Formal analysis**: EMW. **Writing - Original Draft**: EMW, CB. **Writing - Review & Editing**: EMW, HGJ, MK, GLM, CB. **Visualisation**: EMW. ***Funding acquisition***: GLM.


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## Declaration of Competing Interests

EMW, HGJ, MK have no conflicts to declare. GLM has received support from: Reality Health, ConnectHealth UK, Seqirus, Kaiser Permanente, Workers' Compensation Boards in Australia, Europe and North America, AIA Australia, the International Olympic Committee, Port Adelaide Football Club, Arsenal Football Club. Professional and scientific bodies have reimbursed him for travel costs related to presentation of research at scientific conferences/symposia. He has received speaker fees for lectures on pain and rehabilitation. He receives book royalties from NOIgroup publications, Dancing Giraffe Press & OPTP. CB has received support from Workers' Compensation Boards in Australia. All remaining authors declare no potential conflicts of interest (personal or financial) with respect to the research, authorship, and/or publication of this manuscript. CB has received support from Return to Work South Australia, South Australian Health Department, and Kaiser Permanente and speaker fees for lectures on pain and rehabilitation.


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## Data Availability

All data and code are available at the Open Science Framework Repository (10.17605/OSF.IO/TMQ3W)

## Supplementary Material

Supplementary Table 1 – PRISMA 2020 for Abstracts Checklist

| Section and Topic | Item # | Checklist item | Reported (Yes/No) |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | No |
| **BACKGROUND** | | | |
| Objectives | 2 | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | Yes |
| **METHODS** | | | |
| Eligibility criteria | 3 | Specify the inclusion and exclusion criteria for the review. | No |
| Information sources | 4 | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | No |
| Risk of bias | 5 | Specify the methods used to assess risk of bias in the included studies. | No |
| Synthesis of results | 6 | Specify the methods used to present and synthesise results. | Yes |
| **RESULTS** | | | |
| Included studies | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | No |
| Synthesis of results | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | Yes |
| **DISCUSSION** | | | |
| Limitations of evidence | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision). | Yes |
| Interpretation | 10 | Provide a general interpretation of the results and important implications. | Yes |
| **OTHER** | | | |
| Funding | 11 | Specify the primary source of funding for the review. | No |
| Registration | 12 | Provide the register name and registration number. | No |

Supplementary Table 2 – PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Page # |
|---|---|---|---|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review. | 3 |
| ABSTRACT | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | 1 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 3-4 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 3-4 |
| METHODS | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 4-5 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 4-5 |
| Search strategy | 7 | Present the full search strategies for all databases, registers, and websites, including any filters and limits used. | 25-26 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 5 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 5-6 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 5-6 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 5-5 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 5 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 5-6 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | 5-6 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 6-7 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 5-6 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 5-6 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | 6-8 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 8 |
| Reporting bias | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 5, 21 |

| | | | |
|---|---|---|---|
| assessment | | | |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 10-11 |
| RESULTS | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 9-10 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | 10 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | 9-11 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | 11 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | 11-13 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 9, 10 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 11-13 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 11-13, 14-16 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | 8-10 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 10-11 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 14-15 |
| DISCUSSION | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 20-21 |
| | 23b | Discuss any limitations of the evidence included in the review. | 21-22 |
| | 23c | Discuss any limitations of the review processes used. | 21-22 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | 22-23 |
| OTHER INFORMATION | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | 4 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 4 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | 4 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 24 |
| Competing interests | 26 | Declare any competing interests of review authors. | 24 |
| Availability of data, code, and other materials | 27 | Report which of the following are publicly available and where they can be found template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | 24 |

Supplementary Table 3 – Database search strategy

| | |
|---|---|
| **Medline** | 1. Evoked Potentials/<br>2. Event-Related Potentials/<br>3. 1 or 2<br>4. Heart Rate/<br>5. 3 and 4<br>6. (Cardiac-afferent signal* or cardio-afferent signal* or Heart?beat-evoked potential? or heart?rate-evoked potential? or heart? beat?-evoked potential? or heart? Rate?-evoked potential? or Heart?beat-evoked response? or heart?rate-evoked response? or heart?beat evoked potential* or heart? beat?-evoked response? or heart? Rate?-evoked response?).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]<br>7. ((Heart beat* or Heart?beat* or Heart rate* or Heart?rate or cardiac or cardio) adj3 (evoked potential? or evoked response? or event-related potential? or event related potential? or Evoked brain? Potential? or afferent signal* or scalp potential? or "Neural response? to")).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]<br>8. 5 or 6 or 7<br>9. (amplitude? or latenc* or latent or wave* or magnitud*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]<br>10. 8 and 9<br>11. limit 10 to humans<br>12. limit 10 to animals<br>13. 10 not 12<br>14. 11 or 13 |
| **Scopus** | ( TITLE-ABS-KEY ( amplitude* OR latenc* OR latent OR wave* OR magnitud* ) ) AND ( ( TITLE-ABS-KEY ( "Cardiac-afferent signal*" OR "cardio-afferent signal*" OR "Heart-beat-evoked potential*" OR "Heartbeat-evoked potential*" OR "heart-rate-evoked potential*" OR "heartrate-evoked potential*" OR "heart* beat-evoked potential*" OR "heart* beatevoked potential*" OR "heart* Rate-evoked potential*" OR "heart* Rateevoked potential*" OR "Heart-beat-evoked response*" OR "Heartbeat-evoked response*" OR "heart-rate-evoked response*" OR "heartrate-evoked response*" OR "heart-beat evoked potential*" OR "heartbeat evoked potential*" OR "heart* beat-evoked response*" OR "heart* Rate-evoked response*" OR "heart* Rateevoked response*" ) ) OR ( TITLE-ABS-KEY ( ( "Heart beat*" OR heartbeat* OR heart-beat OR "Heart rate*" OR heart-rate OR heartrate OR cardiac OR cardio ) W/3 ( "evoked potential" OR "evoked potentials" OR "evoked response*" OR "event-related potential" OR "event-related potentials" OR "event related potential" |

| | |
|---|---|
| | OR "event related potentials" OR "Evoked brain* Potential" OR "evoked brain* potentials" OR "afferent signal*" OR "scalp potential" OR "scalp potentials" OR "Neural response to" OR "Neural response to" ) ) ) ) |
| **PsycINFO** | 1. Evoked Potentials/<br>2. Heart Rate/<br>3. 1 and 2<br>4. (Cardiac-afferent signal* or cardio-afferent signal* or Heart?beat-evoked potential? or heart?rate-evoked potential? or heart? beat?-evoked potential? or heart? Rate?-evoked potential? or Heart?beat-evoked response? or heart?rate-evoked response? or heart?beat evoked potential* or heart? beat?-evoked response? or heart? Rate?-evoked response?).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]<br>5. ((Heart beat* or Heart?beat* or Heart rate* or Heart?rate or cardiac or cardio) adj3 (evoked potential? or evoked response? or event-related potential? or event related potential? or Evoked brain? Potential? or afferent signal* or scalp potential? or "Neural response? to")).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]<br>6. 3 or 4 or 5<br>7. (amplitude? or latenc* or latent or wave* or magnitud*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]<br>8. 6 and 7 |
| **Embase/ Emcare** | 1. Evoked response/<br>2. Event Related Potential/<br>3. 1 or 2<br>4. Heart Rate/<br>5. 3 and 4<br>6. (Cardiac-afferent signal* or cardio-afferent signal* or Heart?beat-evoked potential? or heart?rate-evoked potential? or heart? beat?-evoked potential? or heart? Rate?-evoked potential? or Heart?beat-evoked response? or heart?rate-evoked response? or heart?beat evoked potential* or heart? beat?-evoked response? or heart? Rate?-evoked response?).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]<br>7. ((Heart beat* or Heart?beat* or Heart rate* or Heart?rate or cardiac or cardio) adj3 (evoked potential? or evoked response? or event-related potential? or event related potential? or Evoked brain? Potential? or afferent signal* or scalp potential? or "Neural response? to")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]<br>8. 5 or 6 or 7 |

| | |
|---|---|
| | 9. (amplitude? or latenc* or latent or wave* or magnitud*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]<br>10. 8 and 9<br>11. limit 10 to humans<br>12. limit 10 to animals<br>13. 10 not 12<br>14. 11 or 13 |
| **Cochrane** | #1 MeSH descriptor: [Evoked Potentials]<br>#2 MeSH descriptor: [Heart Rate]<br>#3 #1 and #2<br>#4 (cardiac-afferent NEXT signal*) or (cardio-afferent NEXT signal*) or (Heart-beat-evoked NEXT potential?) or (Heartbeat-evoked NEXT potential?) or (heartrate-evoked NEXT potential?) or (heart-rate-evoked NEXT potential?) or (heart? NEXT "beat-evoked potential") or (heart? NEXT "beat-evoked potentials") or (heart? NEXT "beatevoked potential") or (heart? NEXT "beatevoked potentials") or (heart? NEXT "Rateevoked potential") or (heart? NEXT "Rateevoked potentials") or (heart? NEXT "Rate-evoked potential") or (heart? NEXT "Rate-evoked potentials") or (Heart-beat-evoked NEXT response?) Or (Heartbeat-evoked NEXT response?) or (heartrate-evoked NEXT response?) or (heart-rate-evoked NEXT response?) or ("heartbeat evoked" NEXT potential*) or ("heart-beat evoked" NEXT potential*) or ("heart beatevoked" NEXT response?) or ("hearts beatevoked" NEXT response?) Or ("hearts beat-evoked" NEXT response?) or ("heart beatevoked" NEXT response?) Or (heart? NEXT "beat-evoked response") or (heart? NEXT "beat-evoked responses")<br>#5 ("Heart beat" or "heart beats" or Heart-beat* or heartbeat* or "Heart rate" or "heart rates" or Heart-rate* or heartrate* or cardiac or cardio) NEAR/3 ("evoked potential" or "evoked potentials" or "evoked response" or "evoked responses" or "event-related potential" or "event-related potentials" or "event related potential" or "event related potentials" or "Evoked brain Potential" or "evoked brains potential" or "evoked brain potentials" or "evoked brains potentials" or "afferent signal" or "afferent signals" or "afferent signalling" or "scalp potential" or "scalp potentials" or "Neural response to" or "neural responses to")<br>#6#3 or #4 or #5 |
| **Web of Science** | (TS=(("Heart beat*" OR heartbeat* OR heart-beat OR "Heart rate*" OR heart-rate OR heartrate OR cardiac OR cardio) NEAR/3 ("evoked potential" OR "evoked potentials" OR "evoked response*" OR "event-related potential" OR "event-related potentials" OR "event related potential" OR "event related potentials" OR "Evoked brain* Potential" OR "evoked brain* potentials" OR "afferent signal*" OR "scalp potential" OR "scalp potentials" OR "Neural response to" OR "Neural response to")) OR TS=("Cardiac-afferent signal*" OR "cardio-afferent signal*" OR "Heart-beat-evoked potential*" OR "Heartbeat-evoked potential*" OR "heart-rate-evoked potential*" OR "heartrate-evoked potential*" OR "heart* beat-evoked potential*" OR "heart* beatevoked potential*" OR "heart* Rate-evoked |

| | |
|---|---|
| | potential*" OR "heart* Rateevoked potential*" OR "Heart-beat-evoked response*" OR "Heartbeat-evoked response*" OR "heart-rate-evoked response*" OR "heartrate-evoked response*" OR "heart-beat evoked potential*" OR "heartbeat evoked potential*" OR "heart* beat-evoked response*" OR "heart* Rate-evoked response*" OR "heart* Rateevoked response*")) AND (TS=(amplitude* OR latenc* OR latent OR wave* OR magnitude*)) |

## Supplementary Table 4 – Eligibility Assessment

| | |
|---|---|
| **Inclusion criteria** | Assesses individual humans aged over 18 years |
| | Includes a measure of interoception (as specified by the author) |
| | Provides quantitative outcome of a HEP response |
| **Exclusion criteria** | Non-human, animal participants |
| | Grey literature or secondary data or is a book chapter |

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# Chapter Three

# Minding the body: Interoceptive sensibility is associated with pain impact in people with chronic pain disorders.

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**Key words:** interoception, pain impact, fibromyalgia, complex regional pain syndrome

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## Abstract

Interoception, which is understood as the awareness of bodily sensations, is often disrupted in people living with chronic pain. We examined whether pain impact was related to self-reported interoception, known as interoceptive sensibility, across 260 individuals who lived with fibromyalgia, complex regional pain syndrome, chronic musculoskeletal pain, or considered themselves healthy. Across the groups, individuals with fibromyalgia and complex regional pain syndrome reported higher interoceptive sensibility and pain impact. Across the whole sample, pain impact was positively associated with interoceptive sensibility ($r$ = .609, $p$ < .001). This association was weakest in people with complex regional pain syndrome. These findings demonstrate an association between pain impact and altered interoceptive sensibility across multiple chronic pain conditions. Future research should examine whether interventions that modify interoceptive sensibility reduce the impact of pain on the wellbeing of individuals.

## Introduction

The impact of chronic pain is substantial. Approximately one in five adults report chronic pain, and rates of high impact chronic pain - defined as pain that limits life or work on most or every day of the last three months – approaches one in ten (Nahin et al., 2023). Chronic pain impacts work and life in many ways, including disrupted sleep, impaired cognitive function, mental ill health, and reduced social interactions (Andersen et al., 2014; Bushnell et al., 2013; Fitzcharles et al., 2021). People with chronic pain often report that it is not only their pain that impacts their life and work; there are other bodily feelings that can be distressing (Valenzuela-Moguillansky, 2013), and a growing body of evidence of more widespread disruption to general bodily awareness is emerging across a range of chronic pain disorders (Bowering et al., 2014; G. L. Moseley & Flor, 2012). Further investigation is critical to advance our understanding of the relationship between body awareness and the impact of chronic pain in order to guide therapeutic interventions.

The capacity to monitor and maintain bidirectional communication between the body and the brain is captured by the term interoception. Although there is no single consensus on the precise definition of interoception, it may be variously described in terms of the perception of the physiological condition of the body (Khalsa, Feinstein, et al., 2018). We consider interoception to include the processing of bodily information that promotes both automatic regulation (outside of awareness) and bodily feelings that motivate action, such as thirst and hunger (in awareness) (Williams et al., 2012). An accurate perception of the body is necessary for body regulation. Interoception informs our behaviours and actions, ranging from feeling stiff, noticing a raised heart rate, or responding with a gasp or sigh to regulate carbon dioxide levels, all of which serve to maintain physiological integrity of the body through homeostasis (Chen et al., 2021). That such sophisticated processes can take place without reaching awareness is a testament to the homeostatic capabilities of the interoceptive system operating unconsciously. Further, the ability of interoceptive signals to also elicit conscious, purposeful behaviours highlights the importance of maintaining homeostatic stability through regulated action. Impaired interoception has been linked to a range of psychopathologies (Bonaz et al., 2021; Brewer et al., 2021; Dunn et al., 2007; Khalsa, Feinstein, et al., 2018; Locatelli et al., 2023; Murphy et al., 2019; Nord et al., 2021; Nord & Garfinkel, 2022; Pollatos et al., 2009; Suksasilp & Garfinkel, 2022) and chronic pain (Di Lernia et al., 2016; Gu et al., 2012; Montoya et al., 2005; G. L. Moseley & Flor, 2012; Pace-Schott et al., 2019; Tabor et al., 2017).

One important question that remains unanswered is whether interoceptive sensibility relates to the impact of chronic pain on a person's life. According to a limited cognitive resources model (Eccleston, 1994; Fisher et al., 2018), having a greater focus on bodily processes may increase the impact of chronic pain, since the attention towards the 'body in mind' may reduce available cognitive resources for other cognitive processes. People with chronic pain tend to report that they find it difficult to get their mind *off* what is happening in their body (Crofford, 2015; Guiffrida et al., 2023). The relationship may work the other way too: greater impact of a painful condition on one's life may well lead an individual to focus more intently on bodily feelings as they strive to understand and manage their pain. This illustrates two potential directions of association between interoceptive sensibility and pain impact. In this cross-sectional, observational study, we aimed to determine whether self-reported interoception, known as interoceptive sensibility, is associated with pain impact in people from four separate groups: people living with fibromyalgia, people living with complex regional pain syndrome, people living with another chronic musculoskeletal syndrome, and healthy controls. We also aimed to characterise the relationship between independent demographic variables, wellbeing, affect, pain, and interoceptive sensibility using descriptive and regression analysis.

## Methods

### Sample

A convenience sample of 260 people (227 females, 33 males, and 2 non-binary individuals) across three pain groups (fibromyalgia (FM), complex regional pain syndrome (CRPS), and chronic musculoskeletal pain syndrome (CM)) and a healthy control group (HC) participated (see *Figure 1*). The FM group consisted of 82 participants (80 females, *m* age 42 ± 13 years). The CRPS group consisted of 55 participants (49 females, *m* age 46 ± 13 years). The CM group consisted of 73 participants (60 females, *m* age 49 ± 17 years). The HC group consisted of 50 participants (38 females, *m* age 40 ± 12 years). Seven participants in the CRPS group had comorbid fibromyalgia.

#### Demographic Characterisation

General demographic information and socioeconomic factors (education, employment status, and financial living comfortability) were collected to characterise the groups (see *Table 2*). The Primary Care Post-Traumatic Stress Screen (PC-PTSD) (Prins et al., 2003) is a four-item scale used to assess signs of PTSD. The Pittsburgh Sleep Quality Index

(PSQI) (Buysse et al., 1989) was used to assess sleep quality and disturbances in the previous month. The PSQI comprises 19 self-report questions that tap into one of seven subdomains related to sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Weinstein's Noise Sensitivity Scale is a 21-item scale used to assess individual differences in sensitivity to perceived noises (Weinstein, 1978).

## Primary Outcomes

### Interoceptive Sensibility

The Body Perception Questionnaire-Short Form (BPQ) (Porges, 1993) is a self-report measure that assesses interoceptive sensibility and autonomic nervous system reactivity. While the total BPQ-short form was administered, only the body awareness subscale was included in this analysis, based on previous studies that have employed the BPQ (Betka et al., 2018; Desmedt et al., 2022; Garfinkel et al., 2015; Pearson & Pfeifer, 2022). The questionnaire consisted of 46 items measured on a 5-point Likert scale. In this study, internal consistency was adequate for the BPQ (α = .86, ω = .86) as indicated by Cronbach's alpha and omega coefficients, which was consistent with previous studies (ω = 0.97) (Vig et al., 2022). An example of the BPQ is "*during most situations I am aware of how fast I am breathing*" (Item 6).

### Pain Impact

Subjective assessment of pain impact was performed using the Fibromyalgia Impact Questionnaire – Revised (FIQ-R) (Burckhardt et al., 1991) or an adapted version for other groups. The FIQ-R comprises 21 items and produces a score ranging from 0 to 100; with a higher score indicating that fibromyalgia has a larger impact on an individual's daily functioning. For the non-fibromyalgia groups, the questions were the same, but the word *fibromyalgia* was replaced with *current health issues* or *symptoms* – referred to as the Symptom Impact Questionnaire – Revised (SIQ-R). Hereafter, when referring to the questionnaires collectively, we will use 'F/SIQ-R'.

## Secondary Outcomes

### Multidimensional Assessment of Interoceptive Awareness

A secondary measure of interoceptive sensibility, the Multidimensional Assessment of Interoceptive Awareness Version 2 (MAIA) (Mehling et al., 2018), assesses interoceptive sensibility across eight subscales: noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening, and trusting. The items are scored between 0 and 5, with a higher score indicating greater awareness of bodily sensations. Internal consistency was adequate for the MAIA (α = .74, ω = .8), as indicated by Cronbach's alpha and omega coefficients, which was consistent with previous studies (α range = 0.69 – 0.88 (Vig et al., 2022). An example item of the MAIA is "*I can maintain awareness of my inner bodily sensations even when there is a lot going on around me"* (Item 17).

### Depression, Anxiety and Stress Scale

Depression, anxiety, and stress were assessed using the Depression, Anxiety and Stress scale (DASS) (Lovibond, 1995). The DASS has good internal consistency across the three dimensions (α range = .78 - .89) and good test-retest reliability (*r* = .79) (Brown et al., 1997). An example item on the DASS scale is *"I felt that I had nothing to look forward to"* (Item 10).

### Brief Pain Inventory

A secondary measure of pain, the Brief Pain Inventory (BPI) (Cleeland, 1991), was used to assess the severity of pain and its interference with daily functioning. When used in clinical settings to assess both pain severity and interference, the BPI has shown excellent internal consistency (Valenzuela-Moguillansky et al., 2017). An example of the BPI is "*circle the number that best describes your pain at its worst in the last 24 hours*" (Item 3).

### Pain Catastrophising Scale

The level of catastrophic thinking related to pain experiences was assessed using the Pain Catastrophising Scale (PCS) (Sullivan et al., 1995). It aims to assess how individuals magnify the negative aspects of pain, feelings of helplessness in dealing with their pain, and the level of rumination about their pain. The PSC has excellent internal consistency (α = .95) (Osman et al., 2000) and good reliability with high test-retest reliability (*r* = .88) (Wheeler et al., 2019).

### Central Sensitisation Inventory`

The Central Sensitisation Inventory (CSI) was used to assess the potential existence of central sensitisation via patterns of pain and sensitivity (Neblett et al., 2013). The CSI has good test-retest reliability (*r* = .82) and internal consistency (α = .88) (Mayer et al., 2012).

### Positive Affect Negative Affect Scale

Positive and negative emotional states were assessed using the Positive Affect Negative Affect Scale (PANAS) (Watson et al., 1988). The scale requires individuals to indicate the extent to which they have current feelings of, for example, joy, sadness, and enthusiasm. The PANAS has high internal consistency for both the positive (α = .86 – .90) and negative (α = .84 – .87) subdomains (Magyar-Moe, 2009).

### Procedure

Ethical approval was obtained from the Institutional Ethics Committee (ID: 203294). The online survey used Qualtrics (Qualtrics, Provo, UT, USA), an online survey management application, and was developed and piloted prior to commencing data collection. The survey was advertised primarily online within various public and private chronic pain community channels (Facebook Pages and Groups, Twitter), and previous participants affiliated with the University of South Australia who had consented to be re-contacted for future studies were notified. A screening survey was made accessible via a QR code on the research survey flyer, which was posted around the University. The screening survey outlined the clinical conditions being investigated, assessed the eligibility criteria of living within Australia, aged between 18 and 85 years, and identified as living with one of three clinical conditions (FM, CRPS, CM) or as a healthy individual. The decision to not require a medical diagnosis was intentionally made due to the common difficulties experienced by people with conditions like FM and CRPS, due to the unclear pathological origins and medical stigma associated with invisible illnesses. Chronic cancer-related pain was treated as an exclusion as the mechanisms of cancer pain are not comparable to those of musculoskeletal pain because of the influence of medication and or interventions that confound results.

Eligible participants who passed the screening process were provided a URL to access the group-specific questionnaire. When participants were ready to start the survey, they were asked to read through a participant information document that detailed the study purpose and a statement of ethical approval. To proceed, participants were required to provide informed consent. A brief survey inventory outline was presented before the demographic and wellbeing characteristics were recorded. Three primary research areas (pain, affect,

and interoceptive sensibility) were presented in this sequence; however, the individual inventories were randomised to minimise potential ordering bias. At the completion of the survey, participants were given the opportunity to leave any feedback or further thoughts on the study content, before being offered the chance to win one of ten $40 prepaid VISA cards.

## Reporting the Study

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Elm et al., 2007) checklist and the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (Eysenbach, 2012) were adhered to (see *Supplementary Materials 1* and *2*).

## Data analysis and statistics

All statistical analyses and data visualisation were performed in R version 4.2.1 using RStudio (R Core Team, 2021). The following packages were used: pacman (Rinker, 2019), dplyr (Wickham, 2023a), plyr (Wickham, 2023b), readxl (Wickham & Bryan, 2023), ggplot2 (Wickham, 2016), lattice (Sarkar, 2008), emmeans (Lenth, 2020), lme4 (Bates et al., 2015), lmerTest (Kuznetsova et al., 2017), pbkrtest (Halekoh & Højsgaard, n.d.), tidyverse (Wickham et al., 2019), ggdistgg (Tyner & Wickham, 2021), ggthemes (Arnold, 2020), ggtext (Wilke & Wiernik, 2022), janitor (Firke, 2021), car (Fox & Weisberg, 2019), leaps (Lumley, 2020), mediation (Tingley et al., 2014), viridis (Garnier, 2018), reshape2 (Wickham, 2007), multcomp (Hothorn et al., 2008), caret (Kuhn, 2023), MASS (Venables & Ripley, 2023), gvlma (Pena & Slate, 2019), performance (Lüdecke, n.d.), see (Lüdecke, 2023), correlation (Makowski, 2023), devtools (Wickham, 2022), flexplot (Fife, 2020), and performance (Lüdecke, n.d.).

The data were checked visually, and statistical assumptions were tested using the *gvlma* and *performance* packages in R. ANOVAs were performed to compare the groups for analysis of mean scores across questionnaires. Subsequently, *post hoc* comparisons were conducted using Tukey's HSD test to control for multiple comparisons and identify significantly different pairs of means. The effect sizes for these significant pairings were assessed using Cohen's *d* test, which assigns an effect size of small ($d = 0.2$), medium ($d = 0.5$), or large ($d = 0.8$) (Cohen, 1988). Where data did not satisfy the assumptions of parametric statistics, Kruskal-Wallis one way ANOVA was used.

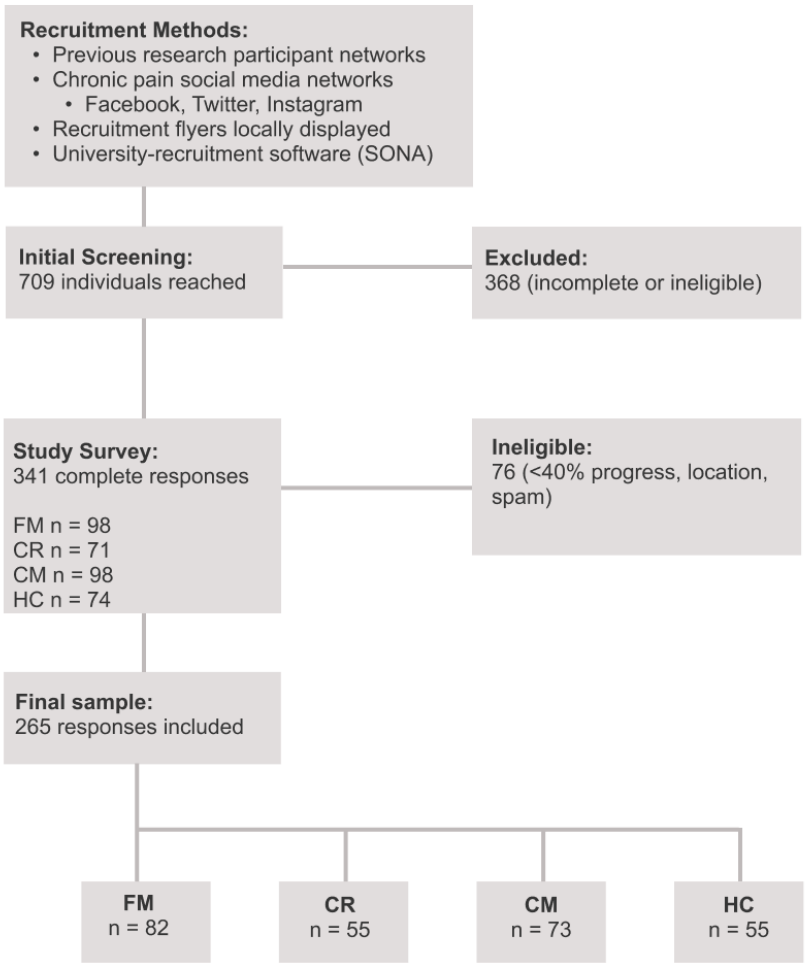



**Figure 1. Recruitment Process**

## Aim 1: Relationship between pain impact and interoceptive sensibility

Pearson correlation analysis was conducted to determine the relationship between pain impact (F/SIQ-R) and interoceptive sensibility (BPQ-Awareness) across groups. Standardised beta coefficients (*β*) were determined for group-specific correlations.

## Aim 2: Characterisation of the dataset and the influence of independent variables on interoceptive sensibility

Linear regression analysis was conducted to investigate whether interoceptive sensibility differed across conditions. The model assumptions were evaluated using the *performance* R package. Group, age, total DASS score, and BPI Interference variables were included as fixed factors in the model. To assess the model fit, the full model was compared to a reduced model in which DASS and BPI were not included (see *Supplementary Table 1*). Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to determine model fit. The final model was selected on the basis of a model with lower AIC and BIC

metrics. We compared the model fit and performed *post hoc* comparisons using pairwise t-tests.

Next, a Pearson correlation was conducted to determine the relationship between all interoceptive sensibility measures (BPQ-Awareness and MAIA) and all pain measures (BPI, PCS, CSI, DASS, and PSQI) across the total sample ($n$ = 260). Correlation coefficients ($r$) and significance values ($p$) were reported in the overall linear correlation, and $p$-values were adjusted for multiple correlations using the Holm-Bonferroni method. The mean ± standard deviation values are reported, unless otherwise stated. Statistical significance was set at $p < .05$.

## Results

A total of 709 individuals were reached by the screening survey; 368 were excluded due to ineligibility (if Australia was not their country of residence) or an incomplete response (< 40% progress). A total of 341 eligible participants remained eligible. A further 76 participants were excluded from the analysis due to incomplete data ($n$ = 35), duplicate entries ($n$ = 3), ineligible location ($n$ = 13), or comorbidities in the HC group that were not listed in the screening ($n$ = 5). This resulted in a final dataset of 260 individuals (FM = 82, CR = 55, CM = 73, and HC = 55) (see *Table 2*) who completed all questionnaires (see *Table 4*).

### Primary Aim: Relationship between pain impact and interoceptive sensibility

Pain impact (F/SIQ-R) was moderately associated with interoceptive sensibility ($r$ = .609, $p < .001$) across the whole sample, indicating that the larger the impact of pain that an individual reports, the more they believe they are aware of their body. Between groups (*Table 1* and *Figure 2*), significant associations were observed in the FM ($\beta$ = 0.57) and CM ($\beta$ = 0.56) groups.

**Table 1. Beta values for each group**

| Group | Unstd. $\beta$ | SE Unstd. $\beta$ | Std. $\beta$ | t | *P* value |
|---|---|---|---|---|---|
| **FM** | 0.178 | 0.029 | 0.567 | 6.164 | < .0001 |
| **CR** | 0.098 | 0.052 | 0.251 | 1.884 | 0.065 |
| **CM** | 0.210 | 0.037 | 0.558 | 5.668 | < .0001 |
| **HC** | 0.189 | 0.076 | 0.338 | 2.482 | < .01 |

**Note:** Unstd. unstandardised, $\beta$ beta, SE standard error, Std. standardised

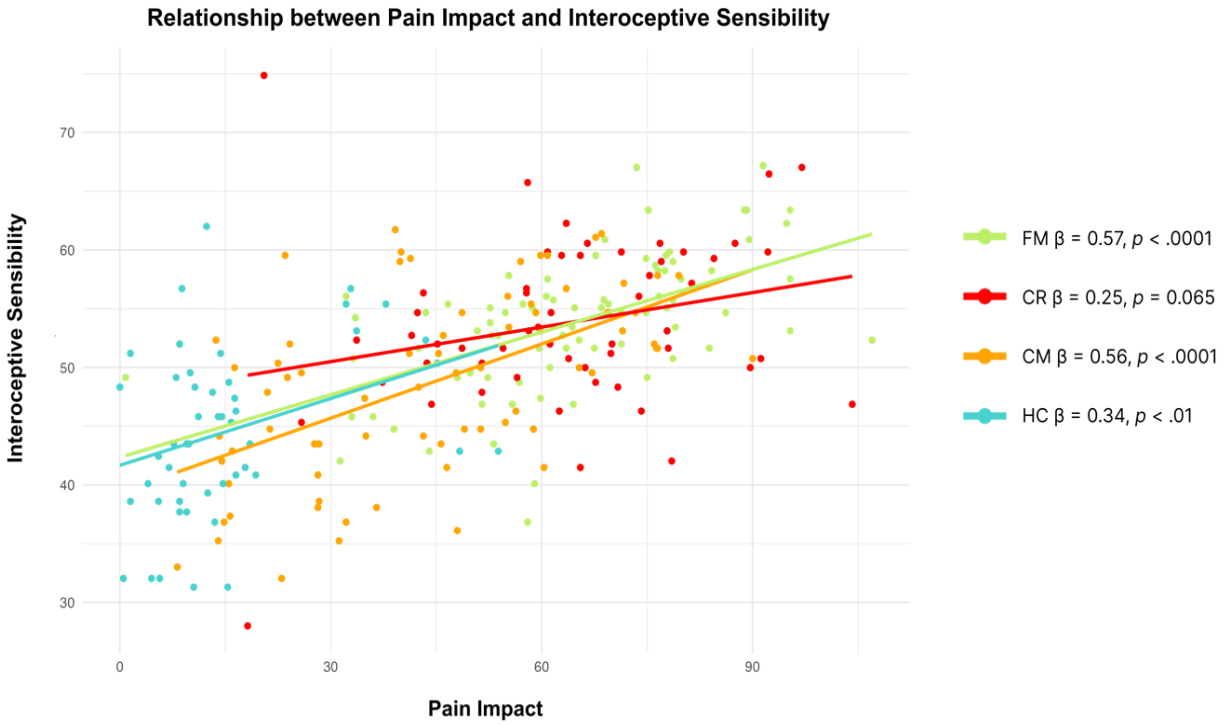



**Figure 2. Relationship between Pain Impact and Interoceptive Sensibility across groups.**

## Table 2. Demographic characteristics

| | FM (*n* = 82) | CRPS (*n* = 55) | CM (*n* = 73) | HC (*n* = 50) |
|---|---|---|---|---|
| **Demographics & wellbeing** | | | | |
| **n (F, M, N.B)** | 82 (80*F,* 2*M*) | 55 (49*F,* 6*M*) | 73 (60*F,* 12*M*, 1*NB)* | 50 (38*F,* 11*M,* 1*NB*) |
| **Mean age (SD)*** | 42.32 ± 13.4 | 45.69 ± 12.82 | 48.85 ± 16.83 | 39.58 ± 12.18 |
| **Handedness (*n*)** | 72 R, 8 L, 2 A | 45 R, 4 L, 6 A | 59 R, 6 L, 8 A | 43 R, 7 L |
| **Healthcare card (*n*)** | 36 | 22 | 22 | 12 |
| **Primary Care PTSD Screen** | 2.10 ± 1.64 | 1.95 ± 1.56 | 1.55 ± 1.56 | 0.98 ± 1.45 |
| **Mean sleep quality** | 12.94 ± 5.25 | 14.71 ± 5.07 | 10.36 ± 4.61 | 6.94 ± 3.68 |
| **Noise Sensitivity (median)**** | 4.00 ± 1.31 | 4.00 ± 1.39 | 4.00 ± 1.05 | 3.08 ± 1.28 |
| **Nicotine use (%)** | 13% | 13% | 7% | 4% |
| **Substance use (%)** | 6% | 11% | 7% | 2% |
| **Education (%)** | | | | |
| **Some high school** | 13% | 2% | 4% | 4% |
| **High school** | 11% | 9% | 8% | 15% |
| **Trade or vocational studies** | 32% | 35% | 19% | 20% |
| **Some university** | 11% | 15% | 19% | 5% |
| **Bachelor's degree** | 22% | 31% | 27% | 22% |
| **Postgraduate degree** | 11% | 9% | 23% | 34% |
| **Employment status (%)** | | | | |
| **Employed** | 65% | 35% | 53% | 89% |
| **Unemployed** | 17% | 31% | 16% | 4% |
| **Unemployed due to health** | 6% | 18% | 5% | 0% |
| **Retired** | 9% | 15% | 19% | 2% |
| **Current student** | 4% | 2% | 5% | 5% |
| **Financial status (%)** | | | | |
| **Finding it difficult** | 34% | 27% | 14% | 2% |
| **Getting by** | 38% | 46% | 44% | 26% |
| **Comfortable** | 28% | 27% | 43% | 73% |

**Note:** *n* total, *F* female, *M* male, *N.B* non-binary, SD standard deviation, ± standard deviation, R right, L left, A ambidextrous, PTSD Post-Traumatic Stress Disorder. *There was a significant difference in age across groups ($F = 5.101$, $p = .001$). Post hoc Tukey tests revealed significant differences between FM and CM ($p < .05$), HC and CM ($p < .01$), and HC and FM ($p < .01$). **Noise sensitivity: Kruskal-Wallis $\chi 2 = 6.96$, $df = 3$, $p$-value = 0.073; Pairwise comparison: FM-CM*, HC-CM*. Postgraduate degree encompasses master's degree, advanced diploma, graduate diploma, and graduate certificate.

Secondary Aim: Characterisation of the dataset and the influence of independent variables on interoceptive sensibility

## Comorbid conditions

Comorbid conditions were reported and categorised across groups (see *Figure 3*). As the F/SIQ-R was originally a FM-specific inventory, two questions were absent from the SIQ-R that were included in the FIQ-R. These pertain to the duration of symptoms experienced and the diagnosis. FM participants reported they had been living with the symptoms of FM for between 1 and 60 years (*m* = 15.66 ± 11.95 years) and had been diagnosed between 0 and 40 years ago (*m* = 9.14, ± 9.12 years). Seven CRPS participants reported living with comorbid FM (CR+FM), and they have been descriptively compared – recognising the limited power of any such *post hoc* comparison, to the four groups on the two primary measures, interoceptive sensibility and pain impact (see *Table 3*). The CR+FM group reported higher interoceptive sensibility and pain impact than the other groups. Our protocol deviated at this point, and we added a sensitivity analysis to determine the effect of comorbid FM in the CRPS group and demonstrated that excluding the CR+FM participants from the CRPS group did not significantly change the relationship (*p* = .94) (see OSF repository for sensitivity analysis).

**Table 3. Descriptive results including the comorbid CR+FM participants**

| | FM (n=82) | CR (n=48) | CR+FM (n=7) | CM (n=73) | HC (n=55) |
|---|---|---|---|---|---|
| **Interoceptive sensibility** | 53.78 | 53.51 | 55.91 | 48.78 | 44.53 |
| **Pain impact** | 64.31 | 61.58 | 79.24 | 44.71 | 15.08 |

**Note:** CR complex regional pain syndrome, FM fibromyalgia, CR+FM comorbid complex regional pain syndrome and fibromyalgia, CM chronic musculoskeletal pain, HC healthy control.

There were more reports of comorbidities across the three chronic pain groups than in the healthy control group. Most notably, among the 82 participants in the FM group, 227 comorbid conditions were reported; some participants listed multiple conditions, whereas others listed none. The comorbid conditions experienced by participants seemed to match the key symptoms and pathological features unique to each condition. For example, the FM group demonstrated high rates of psychiatric and bone/joint/muscle comorbidities, consistent with the most common FM symptoms (Hudson et al., 1992; Kleykamp et al. 2021). The CRPS group had the highest rates of neurological and cardiovascular

comorbidities, and interestingly, seven CRPS participants also reported living with fibromyalgia. The CM group had the highest rates of bone/joint/muscle comorbidities and low rates of neurological and cardiovascular conditions. The HC group had very low rates across all comorbidity groups, with the largest comorbid condition being psychiatric, although this number was significantly lower (n = 3) than that in the chronic pain groups.

## Pain Management

Multidisciplinary and multimodal treatments were recorded for all three pain groups. The healthy control group was asked to report the medications and treatments they would access in the event that they were experiencing pain. As such, the reported pain-specific medication and treatment in the healthy control group could not be equally compared to those in the chronic pain groups.

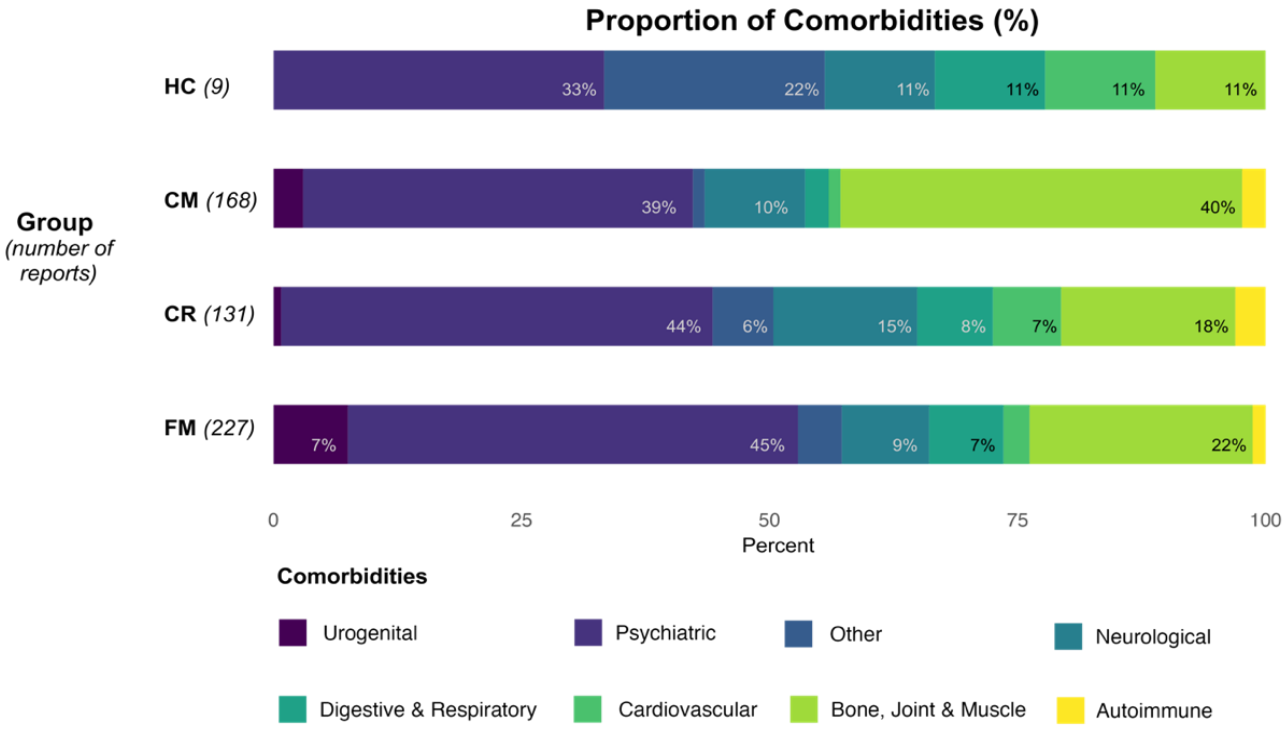



**Figure 3. Proportion of comorbid conditions across groups**

## Pain-specific medication

Pain-specific medications were reported and categorised across groups (see *Figure 4*). The FM group reported high use of antidepressants and opioids, likely for the treatment of psychiatric comorbidities and widespread pain. The CRPS group reported a significantly higher use of opioids for pain management, consistent with the pathological characteristics. The CM group reported the highest use of anti-inflammatory medications, specifically over-the-counter non-steroidal anti-inflammatory drugs. The three pain groups reported moderate use of other medications such as ketamine infusions, spinal cord stimulators, and cannabidiol oil. Opioid antagonists were reported in both CRPS and CM groups. The healthy control group reported minimal use of medication for pain relief, all of which were typically first-line analgesics for short-term pain relief.

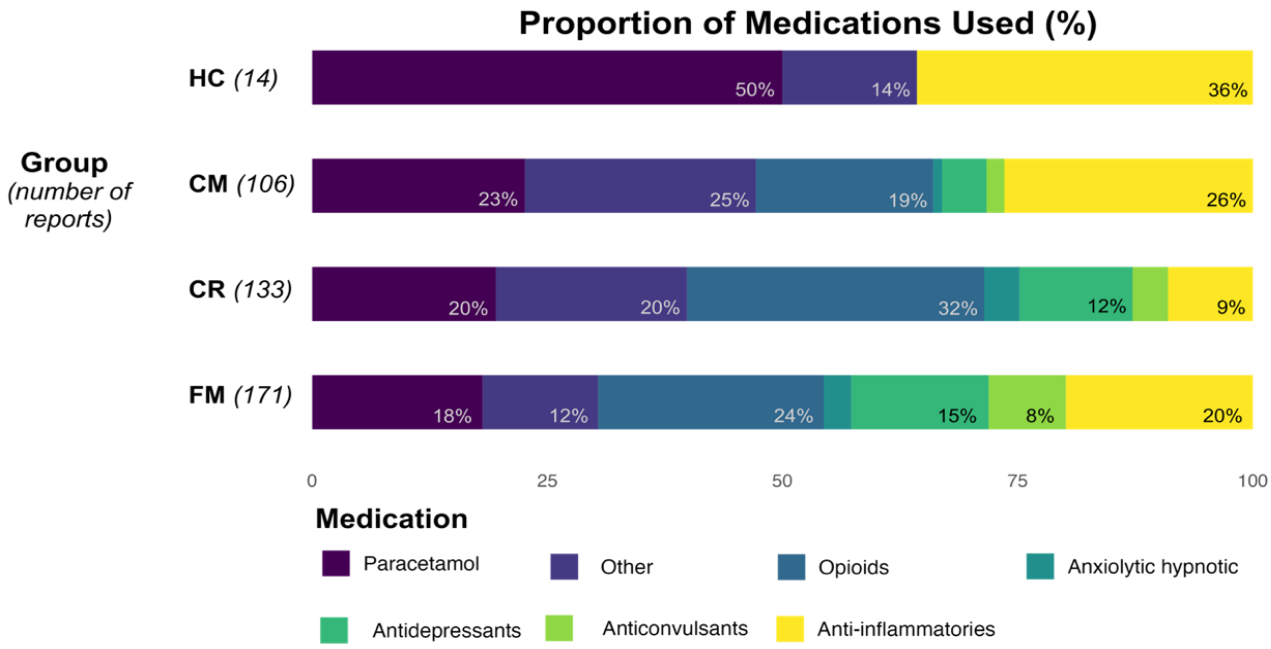



**Figure 4. Proportion of pain-specific medication frequency across groups**

Pain-specific treatment

Pain-specific treatments were reported and categorised across groups (*Figure 5*) (see *Supplementary Table 2)*. Treatment use was examined across the four groups. The FM group displayed high rates of physical and complementary therapies, with minimal reports of surgical or psychosocial treatment approaches. The CRPS group received high levels of surgical treatment and physical therapy with limited complementary or psychosocial therapy. The CM group reported the highest use of physical therapy across the groups, with minimal surgical or psychosocial therapy. Minimal treatment was used in the healthy control group, despite some reports of physical therapy that were typically preventative treatments, such as exercise, massage, and physiotherapy.

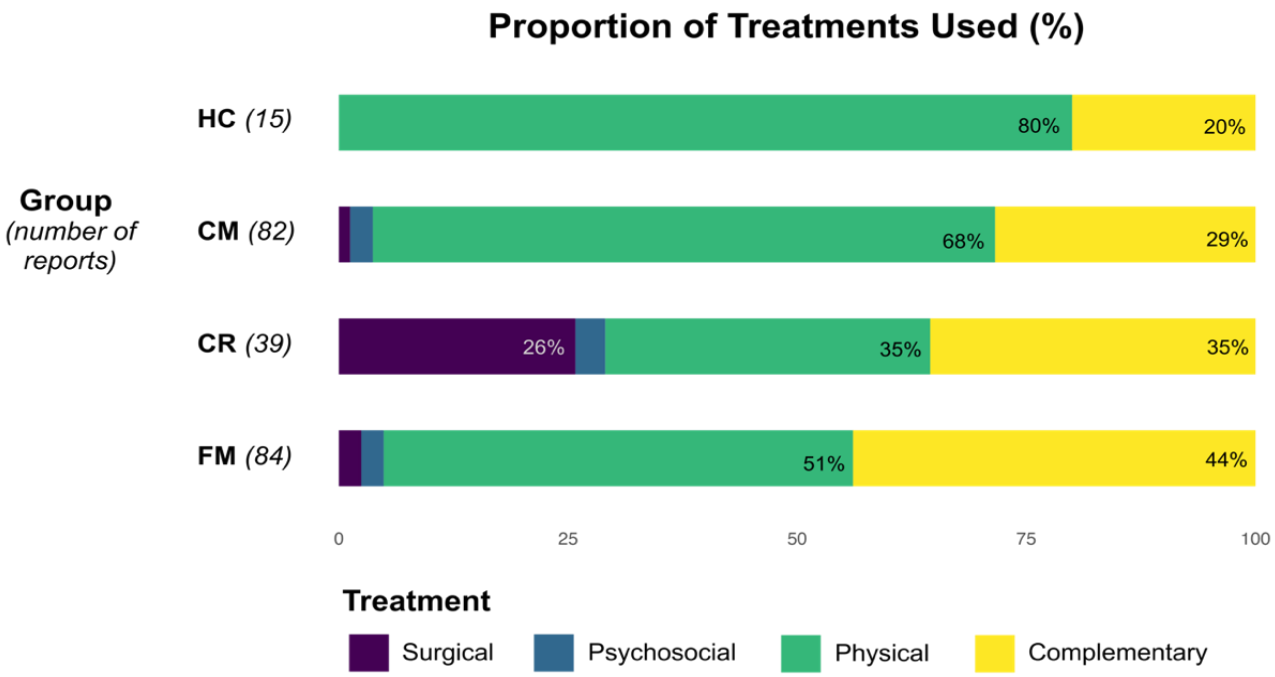



**Figure 5. Proportion of pain-specific treatment frequency across groups**

## Pain Sites

Distinct body mapping of pain across the groups was identified. On an average, the FM and CRPS groups reported the maximum number of pain sites (*n* = 10). The areas that were most commonly associated with pain are shown in *Figure 6*. The reported pain sites generally indicated central and bilateral pain sites in FM (e.g., neck, upper back, lower back, and knees) and, to a lesser extent, in CM, whereas the CRPS group exhibited unilateral pain sites, consistent with diagnostic reports of pain localised to the affected limb. In the absence of chronic pain, the HC group depicted less pain throughout the body, with the most prominent areas being the upper and lower back, consistent with the commonly reported pain sites in healthy individuals (Gilmartin-Thomas et al., 2021; Liebenson, 2004; Natvig et al., 1994).

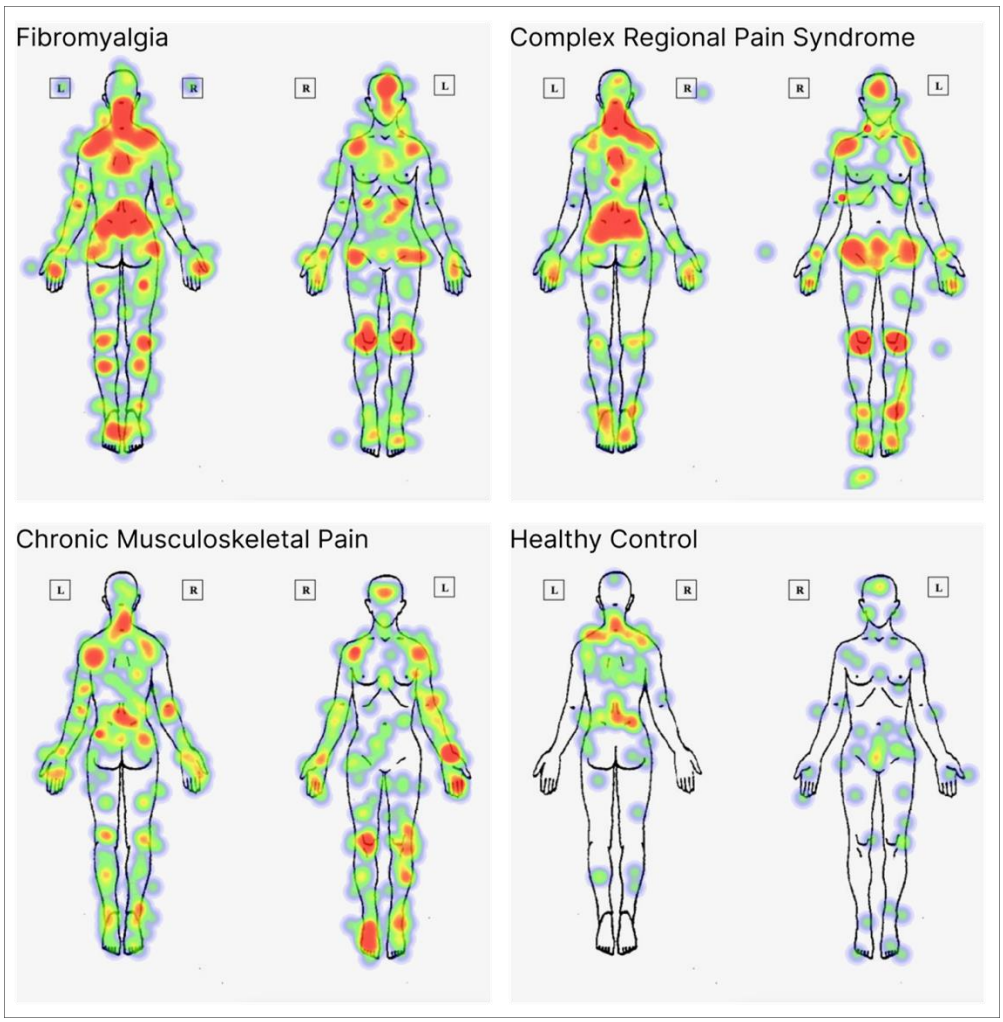



**Figure 6. Body maps depicting pain sites for each group**

**Note:** Colour denotes frequency of sites indicated: red: most frequent.

## Table 4. Descriptive scores across groups

| Factor | Scale | FM | CRPS | CM | HC |
|---|---|---|---|---|---|
| **Pain** | | | | | |
| **F/SIQ-R** | Function | 17.97 ± 6.88 | 17.36 ± 7.76 | 11.48 ± 8.03 | 2.41 ± 3.85 |
| | Overall Impact | 13.24 ± 5.32 | 13.24 ± 6.18 | 8.45 ± 6.32 | 1.34 ± 3.43 |
| | Symptoms | 33.10 ± 8.52 | 33.23 ± 7.67 | 24.77 ± 9.24 | 11.33 ± 7.64 |
| | Total | 64.31 ± 18.48 | 63.83 ± 18.87 | 44.71 ± 20.60 | 15.08 ± 12.74 |
| | Pain sites (median) | 10, IQR 13.50 | 10, IQR 6 | 8, IQR 10 | 1, QR 9.5 |
| | FM years diagnosed | 9.14 ± 9.12 | | | |
| | FM years suffered | 15.66 ± 11.95 | | | |
| **BPI** | Severity | 5.01 ± 2.21 | 6.33 ± 1.77 | 4.81 ± 1.65 | 1.58 ± 1.45 |
| | Interference | 5.73 ± 2.69 | 6.48 ± 2.32 | 4.49 ± 2.11 | 1.69 ± 2.30 |
| **CSI** | Central Sensitisation | 62.39 ± 15.40 | 55.42 ± 15.42 | 45.64 ± 19.56 | 24.50 ± 13.85 |
| **PCS** | Pain Catastrophising | 22.72 ± 12.02 | 21.04 ± 12.79 | 17.29 ± 12.09 | 7.54 ± 8.10 |
| **Affect** | | | | | |
| **DASS** | Depression (median) | Med 7, R 0-21 | Med 7, R 0-21 | Med 6, R 0-18 | Med 1.5, R 0-16 |
| | Anxiety (median) | Med 6.5, R 0-19 | Med 6, R 0-19 | Med 3, R 0-18 | Med 1, R 0-13 |
| | Stress (median) | Med 10, R 1-21 | Med 8, R 0-19 | Med 7, R 0-16 | Med 4, R 0-16 |
| | Overall (median) | Med 49, R 12-96 | Med 46, R 10-102 | Med 32, R 4-78 | Med 16, R 0-66 |
| **PANAS** | Positive (median) | 18.50, R 0-42 | 23.00, R 0-42 | 24.00, R 10-49 | 21.50, R 0-44 |
| | Negative (median) | 16.00, R 0-41 | 17.00, R 0-42 | 14.00, R 10-34 | 11.50, R 0-32 |
| **Interoceptive Sensibility** | | | | | |
| **MAIA** | Noticing | 3.38 ± 1.01 | 3.35 ± 1.20 | 2.97 ± 1.19 | 2.49 ± 1.36 |
| | Not-Distracting | 1.61 ± 0.96 | 1.47 ± 0.86 | 1.59 ± 0.97 | 2.26 ± 0.99 |
| | Not-Worrying | 2.64 ± 0.94 | 2.85 ± 0.90 | 3.17 ± 0.94 | 3.18 ± 1.04 |
| | Attention Regulation | 2.54 ± 1.02 | 2.74 ± 0.99 | 2.55 ± 1.03 | 2.49 ± 1.17 |
| | Emotional Awareness | 3.05 ± 1.00 | 3.13 ± 1.20 | 2.86 ± 0.99 | 2.85 ± 1.43 |
| | Self-Regulation | 2.25 ± 1.17 | 2.47 ± 1.15 | 2.32 ± 1.17 | 2.66 ± 1.25 |
| | Body Listening | 2.33 ± 1.24 | 2.39 ± 1.38 | 2.07 ± 1.12 | 2.03 ± 1.53 |
| | Trusting | 2.09 ± 1.32 | 2.31 ± 1.41 | 2.38 ± 1.17 | 3.09 ± 1.42 |
| **BPQ** | Awareness | 53.78 ± 5.78 | 53.81 ± 7.37 | 48.78 ± 7.77 | 44.53 ± 7.15 |
| | Supradiaphragmatic | 55.79 ± 7.80 | 54.94 ± 6.66 | 51.63 ± 10.21 | 45.51 ± 7.57 |
| | Subdiaphragmatic | 56.39 ± 6.91 | 54.75 ± 9.05 | 51.31 ± 6.87 | 45.84 ± 5.88 |

## Questionnaires

### Pain

#### F/SIQ-R

Significant differences were found between the groups across all FIQR subscales: *Function*: $F$ (3, 261) = 60.62, $p < .001$; *Impact*: $F$ (3, 261) = 58.21, $p < .001$; *Symptoms*: $F$ (3, 261) = 84.04, $p < .001$; *Total Impact*: $F$ (3, 261) = 90.1, $p < .001$. Post hoc Tukey tests revealed significant differences between all group pairs ($p$ <.001) for the *Function* and *Impact* subscales. For *Symptoms*, the HC group reported fewer symptoms than the pain groups (all $p < .001$). Between the pain groups, significant differences emerged between the CM group and both CR and FM groups (all $p < .001$). For *Total Impact*, significant differences (all $p <$ .001) were found between the HC and all pain groups (FM $d$ = -3.10, CR $d$ = -3.03, CM $d$ = 1.73), and between the CM group and other pain groups (CR $d$ = 0.97; FM $d$ = 1.002).

#### BPI

There was an overall significant difference in the BPI severity scores between the groups ($F$ (3, 242) = 50.37, $p < .001$). Post hoc Tukey tests revealed that the CRPS group reported significantly higher pain severity than the FM and CM groups ($p < .001$). The HC group reported significantly lower pain severity than the FM and CR group ($p < .001$). The FM and CM groups did not differ significantly in terms of pain severity ($p = .90$). There was an overall significant difference in the BPI interference scores between the groups ($F$ (3, 238) = 32.26, $p < .001$). Post hoc Tukey tests revealed significantly higher pain interference in the CR, FM, and CM groups than in the HC group ($p < .001$), and, within the pain groups, pain interference was higher in the FM and CR groups than in the CM group ($p < .001$). No difference was found between the FM and CR groups ($p = .2786$).

#### CSI

There was a significant difference in the CSI scores between the groups ($p < .001$). Post hoc Tukey tests revealed significant differences between all groups ($p < .0055$), with higher CSI scores in fibromyalgia (FM) and CRPS groups than in the CM and HC groups.

### PCS

A significant difference was found in the PCS scores across the groups ($p < .001$). Post hoc Tukey tests indicated significantly higher PCS scores across all pain groups compared to the HC group (all $p < .001$). No significant differences were found between the pain groups ($p > 0.05$).

## Interoceptive Sensibility

### BPQ

Significant differences were found between groups across all BPQ subscales: *Awareness*: $F$ (3, 261) = 23.75, $p < .001$; *Subdiaphragmatic*: $F$ (3, 261) = 24.54, $p < .001$; *Supradiaphragmatic*: $F(3, 261) = 17.96$, $p < .001$. Post hoc Tukey tests showed lower scores in the HC group across all BPQ subscales than in the pain groups (all $p < .001$).

### MAIA

There was a significant difference across groups for the *Not-Worrying* ($F = 5.308$, $p = .001$), *Not-Distracting* ($F = 7.396$, $p < .001$), and *Trusting* ($F = 6.108$, $p < .001$) subdomains of the MAIA. Post hoc tests revealed *Not-Worrying* differences between FM and CM ($p < .01$) and HC and FM ($p < .01$). The HC group scored lower than the pain groups in both the *Not-Distracting* and *Trusting* subdomains (all $p < .001$).

## Affect

### DASS-21

*Depression* scores differed significantly between the groups ($\chi2 = 35.72$, $p < .001$), with lower scores in the HC group than in the pain groups, and between the CM and FM groups. *Anxiety* scores also differed significantly ($\chi2 = 47.66$, $p < .001$), with differences between the HC group and all pain groups, as well as between each pain group. *Stress* scores were significantly different ($\chi2 = 43.9$, $p < .001$), with differences between the HC group and all pain groups, as well as between the FM and CM group. *Overall* DASS scores significantly differed ($\chi2 = 71.46$, $p < .001$), with lower scores in the HC group than in the pain groups, between the FM and CM group, and between the CR and CM group.

### PANAS

Significant differences in *Positive* PANAS ($\chi 2 = 15.88$, $p < 0.01$) and *Negative* PANAS ($\chi 2 = 19.003$, $p < .001$) were found. Post hoc tests revealed significant differences between CM-FM for *Positive* ($p < .001$) and FM-HC and CR-HC for *Negative* ($p < .001$) subdomains.

## Secondary Analyses

### Interoceptive sensibility across groups

We found a main effect of interoceptive sensibility across groups ($F = 24.471$, $p < .001$). Post hoc comparisons confirmed a significant difference in awareness between the HC and FM groups ($d = .81$, $p = .031$), and a difference approaching significance between the HC and CRPS groups ($d = .17$, $p = .051$) (see *Figure 7*).

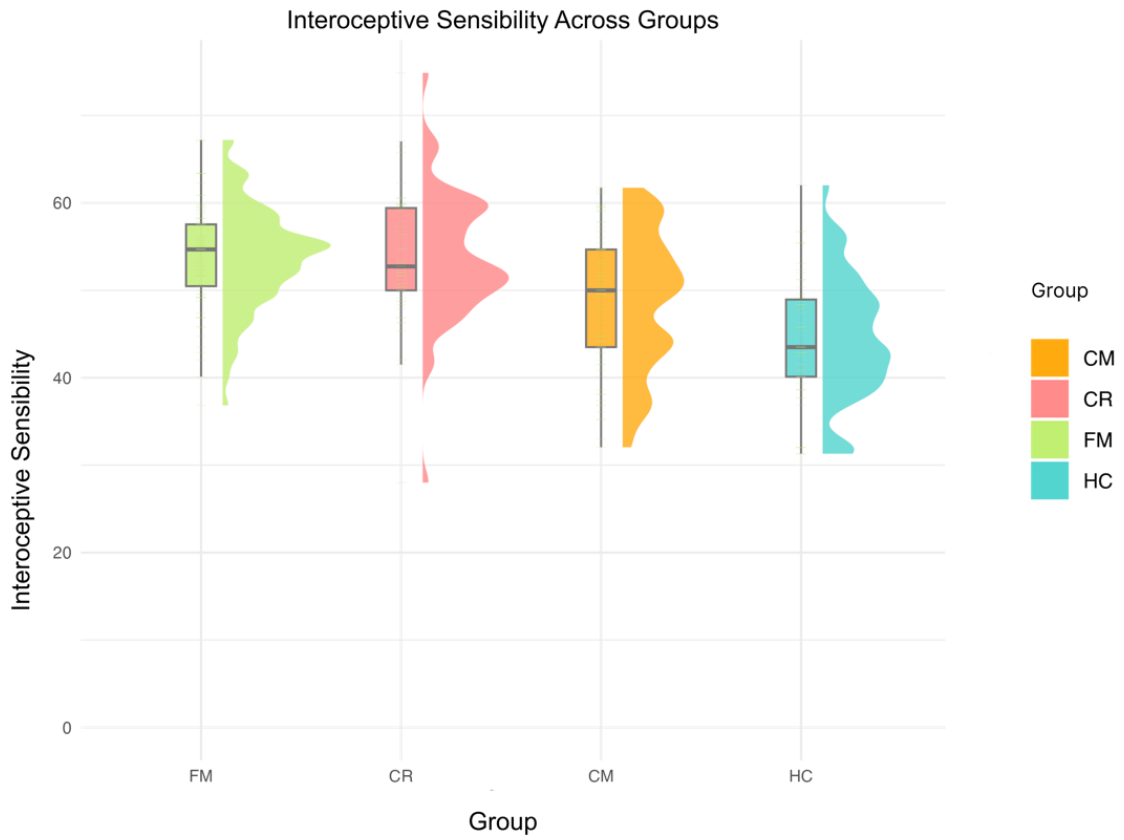



**Figure 7. Interoceptive sensibility across groups**

### Correlation coefficients between interoceptive sensibility and demographic scores

Correlations (see *Table 5*) demonstrated significant positive associations between interoceptive sensibility (BPQ) and pain severity (BPI-Severity, $r = .298$, $p < .001$), pain interference (BPI-Interference; $r = .455$, $p < .001$), central sensitisation (CSI, $r = .696$, $p < .001$), pain catastrophising (PCS; $r = .486$, $p < .001$), and overall score on the DASS ($r = .458$, $p < .001$).

**Table 5. Pearson correlation between interoceptive sensibility and pain across 260 subjects**

| | | BPI-S | BPI-I | CSI | PCS | DASS | Sleep |
|---|---|---|---|---|---|---|---|
| **BPQ** | Awareness | 0.298[a] | 0.455[a] | 0.696[a] | 0.486[a] | 0.458[a] | -0.069[a] |
| **MAIA** | Noticing | 0.208[b] | 0.357[a] | 0.392[a] | 0.267[a] | 0.219[a] | 0.251[a] |
| | Not-distracting | -0.199[b] | -0.176[b] | -0.275[a] | -0.154[c] | -0.108 | -0.167[b] |
| | Not-worrying | -0.141[c] | -0.301[a] | -0.363[a] | -0.567[a] | -0.297[a] | -0.271[a] |
| | Attention Regulation | -0.027 | 0.049 | 0.024 | -0.102 | -0.121 | -0.052 |
| | Emotional Awareness | 0.033 | 0.159[c] | 0.128[c] | 0.024 | 0.069 | -0.004 |
| | Self-Regulation | -0.092 | -0.067 | -0.161[c] | -0.182[c] | -0.115 | -0.114 |
| | Body Listening | 0.130[c] | 0.203[b] | 0.170[b] | 0.071 | 0.029 | 0.086 |
| | Trusting | -0.189[b] | -0.199[b] | -0.284[a] | -0.286[a] | -0.163[c] | -0.215[a] |

**Note:** Holm-Bonferroni adjusted p-values. $p < .0001$ [a], $p < .001$[b], $p < .01$[c]

## Discussion

We aimed to determine the relationship between pain impact and interoceptive sensibility across pain conditions and healthy people. Our findings are consistent with evidence of interoceptive dysregulation in chronic pain disorders (Eccleston, 1994; Lewis & Schweinhardt, 2012; L. G. Moseley, 2008; Ribera d'Alcalà et al., 2015; Tsay et al., 2015; Valenzuela-Moguillansky, 2013; Valenzuela-Moguillansky et al., 2017). Overall, there was a moderately positive association between pain impact and interoceptive sensibility. Interoceptive sensibility was most strongly associated with pain impact in the FM and CM groups, whereas the CRPS group had the least association. Interoceptive sensibility was higher in the FM group than in the healthy controls, with a trend towards higher scores in the CRPS group than in the controls. Even after controlling for depression, anxiety, pain interference, and age, these differences remained evident.

The cross-sectional nature of this study does not allow us to make definitive conclusions about the direction or causality of the relationship between pain impact and interoceptive sensibility. Both directions would be theoretically possible – that the experience of chronic pain may disrupt interoceptive processing, but equally, that pre-existing interoceptive deficits may act as a predisposing risk factor for greater pain impact. It is also plausible that the relationship is epiphenomenal, both being driven by other factors and not directly influencing

each other. We would not expect such variability in the relationship across the sample, which suggests that there are at least multiple factors at play or that there is a causal link between the two variables. A multifactorial relationship would also explain the presence of outliers, such as one individual with CRPS who reported abnormally high interoceptive sensibility and yet abnormally low pain impact. The relationship between pain impact and interoceptive sensibility is likely bidirectional and interdependent in nature; longitudinal research may clarify the nuanced mechanisms linking both factors.

Differences between the groups may reflect the localised nature of CRPS, which is often confined to one limb, as compared to the widespread nature of pain in FM and CM. This suggests differing underlying pain mechanisms and may point to other factors contributing to the weaker association between pain impact and interoceptive sensibility. For instance, it is important to consider that the CRPS group reported, on average, poorer sleep, lower employment rates, more radical treatments, and higher opioid use than the other groups. Pain-related sleep disturbance is highly prevalent in people with CRPS, and the resulting sleep disturbance exacerbates pain in a vicious cycle (Santos et al., 2023; Sun et al., 2021). Similarly, pain hinders work duties and often leads to work absences or unemployment (Bean et al., 2016; Piper et al., 2023), which in turn perpetuates the impact of pain through the physical, psychosocial, and economic consequences associated with job loss.

A sensitivity analysis confirmed that the relationship between pain impact and interoceptive sensibility remained consistent regardless of whether we included the seven CRPS participants who also reported having FM, suggesting that the association between interoceptive sensibility and pain impact does not rely heavily on this small subset of participants. However, that their pain impact scores were substantially higher than the scores for both the CRPS and FM groups clearly suggests that having both conditions is associated with both a greater impact and greater disruption of interoceptive sensibility. This is consistent with Ten Brink et al. (2020) who found that people living with both, CRPS and fibromyalgia, did not report higher pain than either condition alone, but they did report an increase in changes to movement and biological responses, reflecting the greater impact of pain. This indicates that for people living with both FM and CRPS, the degree to which pain impacts daily activities and quality of life may matter more than pain severity alone. While the small sample size of the current study prevents strong conclusions, the results anecdotally fit the pattern of greater pain impact without greater pain severity in people with both FM and CRPS. Ultimately, further research using longitudinal and experimental

designs is required to clarify the relationship between pain impact and interoceptive sensibility.

The pain locations illustrated in the body maps were consistent with expected clinical presentations unique to each chronic pain disorder, validating the accuracy of the clinical diagnoses across groups. Each group displayed distinct clinical profiles – fibromyalgia with psychiatric and neurological comorbidities, high antidepressant use, and complementary treatments; CRPS with neurological and cardiovascular comorbidities and surgical interventions, reflecting targeted nerve pathology treatment; and chronic musculoskeletal pain with related musculoskeletal comorbidities, anti-inflammatory medications, and physical therapy, consistent with the musculoskeletal and inflammatory pain mechanisms. While these clinical profiles may partly reflect condition-specific treatment approaches, the consistent relationship between pain impact and interoceptive sensibility across groups implies that addressing interoceptive sensibility could offer a novel therapeutic target for improving outcomes across varied chronic pain states, despite their distinct underlying pathologies. Together, these results demonstrate that both shared and distinct pathways underlie different chronic pain states.

Chronic pain often impairs functioning across physical, cognitive, emotional, and social domains (Walia et al., 2019). This suggests that alterations in the perception and integration of internal body signals in people with chronic pain may contribute to their pain and disability. The association between pain impact and interoceptive sensibility suggests that the disruption of interoceptive processing may be a mutual mechanism underlying both. Assessing interoception in populations with chronic pain may help to identify those who are likely to experience greater disability. Screening tools that measure interoception may help clinicians address the patient's presentation by retraining interoceptive processes (Bravo et al., 2019; Coggins et al., 2023; Halicka et al., 2020; Lewis et al., 2011; Tahran et al., 2023). Investigating whether manipulating bodily awareness impacts functioning and quality of life beyond just pain severity could provide critical insights (Schmitt & Schoen, 2022). Interoceptive interventions such as bodily illusions (Donegan et al., 2022; Goudman et al., 2022; Khalsa, Hassanpour, et al., 2018; Smith et al., 2021) harness this disruption by manipulating awareness. Matamala-Gomez et al. (Matamala-Gomez et al., 2021) demonstrated that bodily illusions such as magnified body parts (Martini et al., 2014; Romano & Maravita, 2014) can modulate internal body representations in people with chronic pain, and effectively reduce pain. Examining whether such bodily manipulations

influence both interoceptive processing and pain impact may reveal broader therapeutic benefits for improving function (Weng et al., 2021), underscoring the importance of assessing changes in pain impact specifically.

This study has several limitations that should be addressed in future research. The cross-sectional design of the study prevents the determination of any causality or directionality between interoceptive sensibility and pain impact, which could be clarified through longitudinal analysis. Experimental manipulation of interoception would also allow probing the direct causal relationship between awareness and pain. Further, self-report measures introduce subjectivity, and while this is a necessary component of this research, more objective physiological measures may help validate these findings. Equally, qualitative research has a potential advantage to explore lived experience in a way that quantitative analysis cannot, and so while this research consists of self-reported quantitative data, a more robust analysis would incorporate subjective, qualitative data to best capture the lived experience of people living with chronic pain. To build on the current findings, future research should complement subjective measures with objective markers of interoception, such as the heartbeat evoked potential (Kern et al., 2013; Park & Blanke, 2019; Schandry & Montoya, 1996). Using such neural markers may help to determine whether interoceptive deficits in people with chronic pain involve conscious perception or higher-order cortical integration. This approach could potentially inform interoceptive-based interventions aimed at targeting, and perhaps modulating, interoceptive sensibility to reduce the impact of chronic pain.

The findings of this study raise the possibility that disruptions in interoceptive processing contribute to functional disability in individuals living with chronic pain. Clinically, the association between pain impact and interoceptive sensibility suggests that interventions targeting body awareness may benefit patients by reducing the impact of their pain. However, condition-specific variability suggests a need to consider both localised and widespread pain mechanisms when assessing and treating interoceptive deficits. Overall, this study provides preliminary evidence that interoceptive screening tools may assist clinicians in personalising therapies to retrain their abilities and lessen the functional disability experienced by individuals living with pain.

This study found a significant positive relationship between pain impact and interoceptive sensibility, implying potential interoceptive contribution to disability. Variability across

conditions suggests that distinct mechanisms may be involved in localised versus widespread pain. Although limited by its cross-sectional design, these tentative findings indicate that interoceptive-based therapies could help reduce the impact of pain. Future longitudinal and experimental research may clarify directionality and causation between these variables. Nonetheless, this work represents an important first step towards elucidating the role of interoception across chronic pain conditions and highlights the need for personalised interoceptive measurement and treatment approaches.

## Author Contributions

**Conceptualisation:** EMW, MK, GLM, and CB. **Methodology:** EMW, MK, GLM, and CB. **Formal analysis:** EMW. **Writing - Original Draft:** EMW. **Writing - Review & Editing:** EMW, MK, GLM, and CB. **Visualisation:** EMW. **Funding acquisition:** GLM.


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## Declaration of Competing Interests

GLM has received support from: Reality Health, ConnectHealth UK, Kaiser Permanente, Workers' Compensation Boards in Australia, Europe and North America, AIA Australia, the International Olympic Committee, Port Adelaide Football Club, Arsenal Football Club. Professional and scientific bodies have reimbursed him for travel costs related to presentation of research at scientific conferences/symposia. He has received speaker fees for lectures on pain and rehabilitation. He receives book royalties from NOIgroup publications, Dancing Giraffe Press & OPTP. CB has received support from Return to Work South Australia, South Australian Health Department, and Kaiser Permanente and speaker fees for lectures on pain and rehabilitation.

All remaining authors declare no potential conflicts of interest (personal or financial) with respect to the research, authorship, and/or publication of this manuscript.


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## Data Availability

All data and code are available at the Open Science Framework Repository (10.17605/OSF.IO/TMQ3W)

## Supplementary Material

Supplementary Table 1 – Secondary Aim model comparison.

| Model | | AIC | BIC | $R^2$ |
|---|---|---|---|---|
| **Original model** | bpq_aware~group | 1628.298 | 1645.743 | 0.203 |
| **Reduced Model** | bpq_aware~group+age | 1617.626 | 1638.560 | 0.244 |
| **Full model** | bpq_aware~group+age+dass+bpi | 1585.189 | 1613.101 | 0.350 |

Supplementary Table 2 – Pathological characteristics of sample

| | FM | CRPS | CM | HC |
|---|---|---|---|---|
| **Comorbid conditions** | | | | |
| **Psychiatric** | 103 | 57 | 66 | 3 |
| **Neurological** | 20 | 19 | 17 | 1 |
| **Cardiovascular** | 6 | 9 | 2 | 1 |
| **Bone, Joint & Muscle** | 51 | 23 | 68 | 1 |
| **Urogenital** | 17 | 1 | 5 | 0 |
| **Autoimmune** | 3 | 4 | 4 | 0 |
| **Digestive & Respiratory** | 17 | 10 | 4 | 1 |
| **Other** | 10 | 8 | 2 | 2 |
| **Medication for pain** | | | | |
| **Paracetamol** | 31 | 26 | 24 | 7 |
| **Opioids** | 41 | 42 | 20 | 0 |
| **Anti-inflammatories** | 34 | 12 | 28 | 5 |
| **Antidepressants** | 25 | 16 | 5 | 0 |
| **Anticonvulsants** | 14 | 5 | 2 | 0 |
| **Anxiolytic hypnotic** | 5 | 5 | 1 | 0 |
| **Other** | 21 | 27 | 26 | 2 |
| **Treatment for pain** | | | | |
| **Surgical intervention** | 2 | 8 | 1 | 0 |
| **Physical intervention** | 42 | 11 | 55 | 12 |
| **Psychosocial intervention** | 2 | 1 | 2 | 0 |
| **Complementary medicine** | 36 | 11 | 23 | 3 |
| **Surgical intervention** | 2 | 8 | 1 | 0 |

**Note**: All counts are absolute and, account for multiple comorbidities, medications, and treatments per participant.
**Medication**: Anti-inflammatories include both steroidal and non-steroidal anti-inflammatory drugs. 'Other', identified as being reported less than twice, included CBD, immunosuppressants, ketamine, spinal cord stimulator, opioid antagonist, migraine analgesic, palmitoylethanolamide.
**Treatment**: Surgical interventions included transcutaneous electrical nerve stimulation, spinal cord stimulation, and radio frequency ablation. Physical interventions included exercise, thermal relief, compression support, ultrasound, mirror box therapy, hydrotherapy, massage, physiotherapy, podiatry, rheumatology, and exercise physiology. Psychosocial interventions included psychological therapy, counselling, and pain support groups. Complementary interventions included prolotherapy, myotherapy, acupuncture, dry needling, trigger point therapy, chiropractic and osteopathic, osteopathic, yoga, meditation, and rest.
**Comorbidities**: 'Other' comorbidities included skin, genetic, vascular, and hormonal conditions.

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# Chapter Four

*“Under no normal condition is the brain ever excused from receiving continuous reports on the internal milieu and visceral states … the brain is truly the body’s captive audience.”*

Antonio Damasio, 1999.

## 4.1 Thesis Overview

Research increasingly recognises that the processing and perception of internal bodily signals, known as interoception, is disrupted in various psychiatric and medical conditions (Brewer et al., 2021; Murphy et al., 2017; Pollatos et al., 2009). However, precisely how interoception is altered in different patient populations remains unclear. Clarifying these complexities is critical for elucidating the clinical relevance of interoceptive dysregulation. This thesis employed a multi-modal approach to investigate interoception across diverse clinical populations.

One line of research has focused on the heartbeat evoked potential (HEP), a neurophysiological index thought to reflect the cortical processing of cardiac signals (Schandry & Montoya, 1996). As an objective neural marker of interoception that does not require conscious effort, HEP holds promise for revealing potential interoceptive deficits linked to psychopathology. Differences in HEP amplitudes have been found between healthy controls and some clinical groups, although methodological and reporting challenges means that the nature and extent of abnormalities across diverse disorders still requires significant clarification (Coll et al., 2021). One aim of this thesis was to clarify whether HEP systematically differs in various clinical populations, when they are compared with healthy controls. The way our body feels to us reflects another aspect of interoception. This aspect is assessed via self-report. Early studies reporting the extent to which one is aware of bodily signals, known as "interoceptive sensibility", have posited that a heightened interoceptive sensibility may contribute to chronic pain and associated disability. However, few studies have specifically investigated this issue with sufficient samples to allow clear conclusions. Thus, whether interoceptive sensibility is related to pain severity or pain impact, neither or both, remained unanswered. The second study of this thesis specifically explored the association between interoceptive sensibility and pain impact.

Together, these multi-modal approaches highlight interoceptive dysregulation across clinical populations using objective neural signals that “*could serve as biological indicators of disease states*” (Khalsa et al., 2018, p. 508), as well as subjective self-reports that reflect the expression of underlying physiological dysregulation – the ‘lived experience’. Clarifying the complex alterations in interoception through different lenses is critical for understanding its clinical relevance and informing treatments accordingly. These findings stand to inform transdiagnostic interoceptive deficits underlying diverse disorders and guide interoceptive-

based therapies. Ultimately, this thesis contributes important information to the characterisation of interoception in health and disease.

Both chapters examined interoception in a clinical context. *Chapter Two* provided evidence for HEP as an objective neurophysiological marker of cardiac interoception in diverse clinical populations via a systematic and multilevel meta-analytical review. *Chapter Three* examined the relationship between pain impact and interoceptive sensibility by using a cross-sectional self-report design. Taken together, these studies demonstrate atypical interoceptive processing in clinical populations while highlighting dissociations between objective neural measures and subjective self-reports. Clarifying the complexities of altered interoception through multiple lenses is likely to be critical for understanding its clinical relevance and for informing treatment.

## 4.2 Thesis Findings

*Chapter Two* reviewed the literature on HEP in clinical groups and found converging evidence for reduced HEP amplitude in neurological and cardiovascular conditions compared with healthy controls. The lack of consistent findings in psychiatric disorders highlights the need for further research with improved methodological rigour. By clarifying the state of the evidence on HEP across disorders, this review will help guide future research on HEP as a neural marker of interoception, aiding efforts to elucidate the role of interoceptive dysregulation in health and disease. These clinical insights hope to move the field forward by characterising disorders by HEP outcomes and ultimately unravel long-standing questions about mind-body interactions. However, aside from elevating methodological and reporting standards, evaluation of HEP will only ever represent an interoceptive marker one step removed from the lived experience of our body – of feeling it and feeling confident in it.

*Chapter Three* put the focus on how one's body feels. It found a significant positive relationship between pain impact and interoceptive sensibility. This raises the possibility of a potential interoceptive contribution to disability. While this association does not imply causation, it points to the potential role of interoceptive factors in pain-related disability that warrants further investigation. Across the groups, people with fibromyalgia and CRPS reported higher interoceptive sensibility and pain impact.

Yet the relationship between these two assessments was the weakest in people with CRPS. Variability across conditions suggests that distinct mechanisms may be involved in localised versus widespread pain, or perhaps in other distinctions between the conditions, for example no known trigger event (fibromyalgia) or a usually very painful triggering event to a single limb (CRPS). This study suggested, but did not equivocally prove, that personalised interoceptive-based therapies may provide a novel avenue for reducing the impact of pain.

Taken together, both chapters advance the theoretical understanding of the complex role of interoception in health and disease. The discrepancy between objective and subjective assessments of interoception underscores the need to integrate multiple methods to evaluate interoceptive processing comprehensively. The findings revealed system-specific alterations, with deficits emerging only in some disorders. This highlights the importance of assessing multiple physiological pathways to profile interoceptive dysregulation. Variability also suggests that distinct mechanisms may disrupt localised versus widespread bodily representations. These insights pave the way for experimental and clinical research leveraging objective biomarkers to guide personalised interoceptive-based interventions (Heim et al., 2023). Clarifying interoceptive profiles (Oliveira et al., 2022) through a multi-modal lens represents a critical step toward elucidating mind-body interactions and informing integrated treatment approaches.

A key finding of this thesis relates to the complexity of interoception in health and disease and the multiple mechanisms by which it might intersect with pain-related disability. That is, HEP appeared to be systematically affected in a wide range of conditions, not all characterised by bodily awareness disorders, suggesting that one biomarker of HEP can be disrupted without obvious shifts in bodily awareness. Moreover, that the relationship between interoceptive sensibility and pain impact varied according to pain condition suggest multiple factors, not assessed in this thesis, are probably relevant to both how one's body feels, and how one's feeling of one's body impacts life. What is more, perhaps it is the degree to which one's pain impacts life that exerts some disruptive effect on interoceptive sensibility. The potential mechanisms by which such an effect might occur may be simple – more impact, less movement, less activation of interoceptive processes – or complex, where societal expectations around who we are as individuals and the role we play, impacts on how our body feels and how it is monitored. Such complexities will require coordinated and highly controlled interrogation but may well reveal transformative advances in our understanding of our physical and psychological sense of self.

## 4.3 Methodological Implications

Both chapters highlighted important methodological concerns pertaining to interoception research. Standardising protocols and analytical methods for neural markers, such as HEP, will improve reproducibility and clinical applicability. Meanwhile, integrating subjective self-reports with more objective assessments provides complementary insights into the complex, multifaceted nature of interoception. Relying solely on either perspective in isolation risks missing critical nuances regarding how bodily signals shape moment-to-moment experiences.

Any consideration of the wider body of research on HEP must consider its limitations and the methodological challenges that constrain its interpretation. Foremost among these challenges is the extensive physiological noise that confounds the HEP signal itself, specifically cardiac field artefacts, which are electrical potentials generated by the heart (Dirlich et al., 1998), and pulsatile artefacts, which are blood flow pulsations generated through the brain (Kern et al., 2013). These artefacts temporally overlap with HEP. Rigorous separation of the signal from such noise remains a persistent challenge in the field (Coll et al., 2021; Dirlich et al., 1997; Park & Blanke, 2019; Pérez et al., 2005). In addition, the physiological pathways and neural origins underlying HEP remain unclear (Azzalini et al., 2019; Critchley & Harrison, 2013; Silvani et al., 2016). Causal analysis and network-level connectivity have been recommended to better understand specific mechanistic pathways (Park & Blanke, 2019).

One possible factor contributing to the variability in effect estimates, as identified in *Chapter Two*, is the variation in the time windows examined. Nine instances were identified where the authors had restricted their time window of interest to 455-595ms post R-wave, following Dirlich et al. (1998), to minimise cardiac field artefact impact on HEP (Gray & Critchley, 2007; Kern et al., 2013). However, confining analyses to this window risks potentially missing atypical effects outside this range, as evidenced by the findings in the broader 100-600ms window. Given the current lack of evidence on where abnormalities may emerge in clinical groups, analyses spanning broader latencies are essential to fully characterise potential HEP differences. While constraining analyses can reduce artefacts, advanced offline correction methods enable the investigation of the full time course. Indeed, many studies now use cluster-based permutation procedures, an increasingly standard approach in the field (Maris & Oostenveld, 2007; Todd et al., 2021), and one that many authors applied

in *Chapter Two*. In summary, restricting latency analyses to 455-595ms might be sensible for artefact reduction, but it risks overlooking atypical effects in clinical groups. Analyses spanning broader latencies with rigorous artefact corrections are likely to offer optimal sensitivity.

Šoškić et al. (2022) highlighted several key methodological issues highly relevant to the field of HEP. Their multiverse analysis of an EEG dataset demonstrated how even minor variations in data processing and analysis pipelines can dramatically impact study outcomes, even when analysing the same underlying data. They reported large effects of minor procedural deviations, such as determining a low-pass filter, reference electrode, and measurement window, on the N400, which is known to be a large and robust ERP component (Kutas & Federmeier, 2011). Given that HEP is a much smaller signal than many event-related potentials, it may be even more susceptible to the effects of procedural inconsistencies. This likely contributes to the high heterogeneity between HEP studies, as outlined in *Chapter Two*. This indicates a pressing need for the HEP field to adopt standardised methods to improve reproducibility. Extending the multiverse analysis by Šoškić et al. (2022) to HEP could also help systematically evaluate the impact of methodological decisions and identify optimal methods.

*Chapter Two* highlights the importance of standardised methodology, the lack of which is a clear limitation of the field at present. At this stage, the field lacks robust normative HEP data, and a standardised methodological consensus in the field is a necessary step in order to distinguish abnormal HEP. Furthermore, the variability in HEP assessment protocols and parameters limits the comparability of studies and utility of HEP in a clinical setting. The evidence presented sets the groundwork for improved standardised methods in recording HEP, enhancing the reliability and potential clinical utility of this neural marker. Going forward, the HEP field would benefit greatly from establishing consensus recommendations for core assessment tasks and analysis procedures. This approach has recently been developed for EEG research to improve methodological consistency and prevent procedural deviations (Styles et al., 2021). The Agreed Reporting Template for EEG Methodology (ARTEM-IS; Styles et al., 2021) comprises a checklist to standardise protocols, promote transparency, and provide sufficient information for replication. Given the current lack of consensus on assessment protocols, analytical approaches, and normative HEP data, implementing lines of enquiry similar to Šoškić et al. (2022) and adopting methodological

standards akin to the ARTEM-IS guidelines by Styles et al. (2021) would enable accurate interpretations across HEP studies in the future.

Ultimately, the limitations of self-report assessments of interoception underscore the need for a holistic, integrative perspective. Craig (2014) stated that interoceptive signals colour everything: they constantly shape a person's psychological experiences and behaviours. Therefore, the continual effort to remove subjectivity from such tests may be misguided in this case**.** Rather than isolating objective measures, a better approach may be to adopt an integrative approach that accounts for how bodily signals subjectively colour cognition, emotion, and behaviour. This supports evidence that HEP is modulated by various body states, such as attention (Petzschner et al., 2019), arousal (Luft & Bhattacharya, 2015), consciousness (Candia-Rivera, 2022), and hunger (Flasbeck et al., 2021; Lutz et al., 2019; Schulz et al., 2015). At the same time, psychological factors reciprocally shape interoceptive processing. That is, the lived experience of every person affects, and is affected by, interoception.

Interoceptive processing involves complex interactions between subjective experiences, metacognitive awareness, and underlying neural systems. Initial evidence associates subjective and objective assessments in healthy people; however, clinical populations show dissociations, possibly reflecting impaired insight into bodily signals (Brewer et al., 2021; Dunn et al., 2007). For example, sleep disruption, which is common in fibromyalgia, was subjectively scored as worse than that in a healthy sample; however, objective accelerometry and sleep hormone measures did not differ between the two groups (Hinchado et al., 2023). That is, people with fibromyalgia may rate sleep as more disrupted relative to an otherwise equally disturbed objective assessment in healthy individuals. Additionally, Hidding et al. (1994) demonstrated a poor correspondence between subjective functional disability scores in fibromyalgia and objective reports. Valenzuela-Moguillansky et al. (2017) illustrated an overestimation of body size in people with fibromyalgia, which was positively correlated with the impact of pain. Further, Borg et al. (2015) reported heightened intensity ratings to spontaneous sensations that are typically perceived as neutral (e.g., a brush of a feather) in people with fibromyalgia. Generally, these findings provide some evidence of generalised hypervigilance in fibromyalgia; however, other reports have challenged this view. For example, Peters et al. (2000) applied a body scanning reaction time paradigm and found no difference in hypervigilance to innocuous signals between people with fibromyalgia and healthy controls. Hollins et al. (2009) also found no

differences in the intensity reports of sensations evoked by cutaneous and auditory stimuli. Finally, Berryman et al. (2021) found no difference in pre-pulse inhibition (PPI) between people with fibromyalgia and healthy controls. PPI indexes sensorimotor gating, a protective mechanism that filters irrelevant sensory stimulation. The lack of difference in PPI might indicate an intensification of bottom-up signals relevant to pain processing, rather than a generalised hypervigilance to all stimuli.

Given the dissociation between assessment modalities, multimodal research examining links between subjective experiences (interoceptive sensibility), metacognitive appraisals (the correspondence between behavioural and self-report assessments), and neural markers (HEP) across conditions may reveal nuances in how facets of interoception differentiate between health and disease (Khalsa et al., 2018). As Khalsa et al. recommend, "*approaches that perturb the state of the body are recommended, as are convergent approaches such as combined assessments of interoceptive attention and perturbation*" (p. 505). Addressing such questions through combined experiential, behavioural, and neuroimaging assessments may provide clinically relevant distinctions across conditions that can potentially inform biomarker development and interventions targeting identified deficits and dissociations in mind-body integration.

## 4.4 Research Implications

HEP provides a unique window into the brain's representation of bodily signals, something that cannot be accomplished behaviourally. As such, research may examine whether and to what extent HEP responds to experimental manipulation. However, inferring interoception solely from HEP remains speculative, given that HEP is only considered a cardiac interoception marker. This leads us to highlight the need for future research aligning HEP with established interoceptive biomarkers, such as insula activation, and multimodal assessments, such as self-reported interoception. This may guide treatments targeting the transdiagnostic deficits in interoception that potentially underlie psychopathology.

The maladaptive effects of heightened interoceptive sensibility may stem from inaccurate perceptions or mismatched physiological feelings. Predictive processing theory proposes that the brain continually generates predictions about incoming sensory signals (Clark, 2013). These predictions are based on internal models that are updated when errors occur between predicted and actual experiences. The updated models then generate updated predictions (Barrett & Simmons, 2015; Seth, 2013). HEP offers insight into interoceptive

predictions versus errors. Although some propose HEP indicates precision-weighted prediction error signals (Ainley et al., 2016), contrasting perspectives frame HEP as reflecting the predictions themselves (Park & Blanke, 2019; Petzschner et al., 2019). Therefore, an integrative approach measuring illusory effects on both subjective body awareness and objective neural markers (e.g., HEP) could provide meaningful insights into multisensory integration mechanisms. Khalsa et al. (Khalsa et al., 2018) note that "*the most clinically sensitive interoceptive measures might derive from probes that perturb physiological functions to engage specific metacognitive beliefs and/or expectations about bodily states*" (p. 508), underscoring the utility of this approach.

*Chapter Three* of this thesis found a weak correlation between interoceptive sensibility and pain impact in people with CRPS. Michal et al. (2017) reported similar findings, noting positive associations between neglect-like symptoms and anxiety, somatisation, depersonalisation, and pain catastrophising without any association to pain intensity, duration, or disability. This similarity highlights that people with CRPS exhibit various pain-related issues; however, the reported degree of pain may not directly reflect its impact on daily functioning. However, it is also possible that other factors, such as disease duration, mediate this relationship. Bean et al. (2015) found that reports of body perception disturbance, via the Bath CRPS body perception disturbance scale, pain-related factors and functioning were all reduced at a 12-month follow-up after initial diagnosis. This finding highlights the potential confounding role of time in these associations. A significant limitation of *Chapter Three* is the absence of disease duration information captured in the CRPS and CM groups, despite capturing this information in the fibromyalgia group via the FIQ-R. Potential mediating effects of time in the fibromyalgia group are indicated by a small, negative correlation between disease duration and pain impact (note: this correlation analysis was not performed prior to the submission of *Chapter Three* for publication). This suggests that pain impact reports decreased over time, which is similar to the findings of Bean et al. Additionally, Bean et al. (2015) found that people with CRPS and lower baseline anxiety and disability had the lowest reported pain intensity at the 12-month follow-up. This further highlights the role of anxiety and disability in pain-related outcomes, aligning with the high reports of anxiety and daily functioning in *Chapter Three*. Collectively, these findings highlight the need for more holistic assessments of pain that reflect the "*person's unique integration of self-relevant information into their own pain experience*" (Reddan & Wager, 2019, p. 29), as current assessments, such as pain ratings, do not seem to capture the full picture of pain and its impact on the individual's life. Likewise, interoceptive sensibility

assessments (such as the Body Perception Questionnaire; Porges, 1993) may be more appropriately substituted with assessments that explicitly assess the disturbance of body perception, like the recently validated Bath CRPS Body Perception Disturbance Scale (Ten Brink et al., 2021). Finally, standardised patient history assessments that capture duration and related variables would allow for more meaningful interpretation of these data.

Experimentally distorting body perception has been found to correlate with reduced pain intensity. Tactile acuity is compromised in people with chronic pain (Catley et al., 2014), specifically when they are asked to discriminate between two points of stimulation on the painful body part. This distorted perception has been shown to correlate with pain (Moseley et al., 2008). Moseley et al. (2008) demonstrated that tactile stimulation can decrease pain and increase tactile acuity in people with CRPS when they are required to discriminate between the type and location of tactile stimuli, but identical stimulation without that discrimination requirement had no effect. Additionally, Bultitude and Rafal (2010) demonstrated both pain relief and return of function in a CRPS case study through the use of prism adaptation, a therapeutic intervention that experimentally manipulates sensory-motor information. However, a later randomised controlled trial did not find any benefits of the illusion over sham treatments despite finding significant reductions in CRPS pain over time (Halicka et al., 2021). This is interesting, as it potentially points to other factors at play besides the illusion itself, such as a possible placebo effect. Boesch et al. (2016) systematically reviewed the evidence for the effect of bodily illusions on pain and found that resizing illusions that magnified CRPS-affected limbs increased their pain, while minimising the affected limb decreased their pain. Matamala-Gomez et al. (2019) also found increased pain reports when increasing the size of the CRPS-affected limb using immersive virtual reality simulations. Collectively, these findings underscore the adaptive role of interoception in the experience of pain, but equally so point to the potential for bodily illusions to tap into this adaptability to relieve pain experiences.

Recent evidence highlights the dynamic nature of interoceptive perception, which integrates both top-down cognitive expectations (i.e., from higher to lower levels in the processing hierarchy) and bottom-up physiological signals (i.e., from lower to higher levels in the processing hierarchy). Parrotta et al. (2023) investigated whether expecting to feel pain alters the perception of heartbeat frequency. The participants continuously monitored their heartbeat by tapping or counting while awaiting either high- or low-pain electrical stimulation. Participants reported more heartbeats when expecting ‘high-pain’ versus ‘low-pain’ electrical

stimulation, despite no differences in measured heart rate. These findings indicate that pain expectations can induce an illusory perception of an increased heart rate. Further, Iodice et al. (2019) demonstrated that providing faster acoustic feedback of heart rate while cycling on a stationary bike led to an increased rate of perceived exertion. This proof-of-concept study highlights the value of exploring interoceptive illusions that directly target inner body signals to complement interventions that modulate external multisensory perception. These findings demonstrate that interoceptive signals can causally influence pain processing, and that this effect may be mediated by expectancy.

Multisensory illusions have been shown to modulate body representations (Aspell et al., 2013; Suzuki et al., 2013). Park et al. (2016) used VR to manipulate bodily self-consciousness to understand how the brain is modulated by self-identification. They found that conscious self-identification (via self-report) with a virtual body when synchronised to their heartbeat is associated with transient modulations of HEP in the posterior cingulate cortex, but not when the virtual body was asynchronous to their heartbeat. Aligning with Park et al.'s use of VR to modulate bodily self-consciousness, El Ali et al. (2023) developed a method to assess interoceptive accuracy across different modalities (audio, visual, and virtual) and found that, similar to Park et al., including a heartbeat audio signal increased interoceptive sensibility (via the MAIA). Both studies demonstrated the influence of cardiosensory cues (cardio-visual cues in Park et al. and cardio-auditory cues in El Ali et al.) on higher-order representations of bodily and interoceptive perceptions (neural representation in Park et al. and metacognition in El Ali et al.). However, in contrast to Park et al., El Ali et al. found that a greater immersive presence in VR was negatively correlated with interoceptive accuracy. This suggests that top-down factors may interfere with the accurate perception of interoceptive signals in certain contexts. Together, these studies demonstrate the adaptive integration of both top-down and bottom-up bodily signals that contribute to interoceptive function.

Tracking neurophysiological markers such as the heartbeat-evoked potential, complements assessing the effects of bodily illusions on neural oscillations. Recent EEG studies have shown that rubber hand and thermal grill illusions modulate alpha and beta power over frontoparietal regions (Giannopoulos et al., 2022; Rao & Kayser, 2017; Uragami & Osumi, 2023). These oscillatory metrics may quantify interoceptive dysfunction, further motivating EEG monitoring during interoception based interventions for chronic pain.

Virtual reality embodiment shows the potential for modulating interoception in chronic pain conditions such as fibromyalgia and CRPS. Świdrak et al. (2023) found a positive association between virtual embodiment and body perception disturbances in fibromyalgia. That is, people with fibromyalgia who experience more disturbances in their perception of their own body are more likely to have a stronger sense of virtual embodiment in immersive virtual reality. However, the effects were relatively weak, and some participants reported that they did not feel embodied by the avatar because it did not look like them. These limitations suggest that a larger sample of participants with an avatar that closely resembles the participant may strengthen this preliminary finding. These effects are consistent with the analgesia reported in people with CRPS following cardio-visual synchronisation during a heartbeat-enhanced virtual reality experiment (Solcà et al., 2018). Virtual depiction of the affected limb flashing in synchrony with the heartbeat reduced pain ratings, increased heart rate variability, and increased motor limb function. These analgesic effects were absent in the healthy controls and during the asynchronous control condition. Such interoceptive recalibration contrasts daily bodily experiences as "*an unavoidable obstacle, rigid and heavy*" (Świdrak et al., 2023, p. 8).

These findings might be understood within an active inference framework (perception relies on top-down generative models forecasting probable causes of sensations), whereby interoceptive impairment in people with fibromyalgia and CRPS could reflect weaker predictive models that, in a healthy individual, would typically anticipate and accurately explain physiological signals. With less confidence in such top-down representations, external sensory information, like a virtual avatar, may be weighted more heavily. That is, the brain latches onto the avatar as a substitute explanation for its own noisy interoceptive data. This would explain Świdrak et al.'s (2023) finding that greater body perception disturbance is associated with heightened embodiment of virtual avatars, and Solcà et al.'s (2018) reports of reduced pain ratings during cardio-visual synchronisation. This aligns with Arcos-Holzinger et al.'s (2023) report that distinguished immersive VR modalities such as cardiac signalling, body switching, and limb modulation as the most promising approaches for reducing pain and improving body perception disturbance. Preliminary evidence from Kannape et al.'s (2023) proposed augmented reality intervention indicates the potential for providing neurorestorative feedback using principles of visualising interoceptive signals, increasing embodiment through multisensory stimulation, and timing stimulation to the ECG cycle. While further research on virtual embodiment as a model for investigating interoception is warranted, tracking whether boosting precision attenuates virtual

embodiment could determine whether restoring confidence in top-down representations helps reduce pain impact. These insights show promise for investigating interoceptive function using physiological markers, such as HEP.

The predictive coding model proposes that the brain continually generates interoceptive predictions for efficient physiological regulation (allostasis) through an intrinsic allostatic/interoceptive network (Kleckner et al., 2017). Kleckner et al. offered a framework to experimentally perturb interoceptive processes via an "*allostatically challenging task*" (p. 2), where images were presented that would evoke sympathetic nervous system activity, such as arousal. Verdonk et al. (2024) recently showed that modulating cardiorespiratory state via infusions of isoproterenol hydrochloride led to abnormal HEP amplitude in people with generalised anxiety disorder (GAD), with the GAD group yielding a more positive HEP amplitude during the peak period of transient isoproterenol-induced changes and more negative HEP during the early recovery period than healthy controls. These findings suggest that central autonomic hypersensitivity in GAD may involve both bottom-up and top-down processes, linked to abnormal interoceptive processing. Combining experimental perturbations with neural measures (e.g., HEP) and self-reports enables the assessment of the effects on both bottom-up and top-down processes. This multimodal approach may clarify the complex mind-body interactions in chronic pain. Identifying impairments in predictive interoceptive coding and allostatic regulation may reveal novel intervention targets to align physiological states with experiences. Overall, integrating predictive coding principles with experimental, neural, and subjective methods holds promise in elucidating interoceptive disruption in chronic pain.

Given the mounting evidence of interoceptive deficits in chronic pain conditions in *Chapter Three*, CRPS and fibromyalgia may intrinsically produce chronic interoceptive perturbations due to the persistent homeostatic dysfunction they incur - aligning with views of "*chronic pain as a derailed homeostatic process*" (Kent et al., 2021, p. 2). If so, these chronically perturbed conditions would naturally embody the extreme signalling errors predicted by Smith et al. (2021) that impair interoceptive integrity over time: *"interoceptive deficits...manifest most prominently during states of homeostatic perturbation"* (p. 1). In a chronically perturbed interoceptive state, CRPS and fibromyalgia may epitomise contexts predicted to disrupt the brain's interoceptive inferences and allostatic regulation. Clarifying these complex bidirectional links between chronically perturbed homeostatic states and atypical interoceptive processing can reveal new therapeutic targets for chronic pain relief.

## 4.5 Clinical Implications

*Chapter Three* illustrated the high level of comorbid conditions in people living with chronic pain disorders. The three coexisting psychological disorders that were overwhelmingly reported in the chronic pain groups were depression, anxiety, and sleep disorders, all of which were found to be associated with atypical interoception via HEP in *Chapter Two*. Based on the results of *Chapter Two*, it is possible that the comorbidities identified in *Chapter Three* influenced interoception and, as a result, mediated reports of interoceptive sensibility. In depression, diminished interoception corresponds to symptom severity (Pollatos et al., 2009), reduced HEP (Terhaar et al., 2012), and disrupted activity in interoceptive brain regions in response to an interoceptive task (Avery et al., 2014). It is well established that individuals with anxiety-related conditions have higher interoceptive sensibility and accuracy (Domschke et al., 2010; Dunn et al., 2010; Ehlers & Breuer, 1992; Näring & van der Staak, 1995; Pollatos et al., 2007; Van der Does et al., 2000), which is consistent with the neural findings of increased HEP in anxiety-related disorders, potentially reflecting hypervigilance to internal bodily signals at the neural level (Pang et al., 2019; Yoris et al., 2017). Sleep normally reduces interoceptive processing (Mazza et al., 2012), and people with insomnia show heightened HEPs while awake (Wei et al., 2016), and those with nightmares show larger HEPs during REM sleep than during non-REM sleep, reflecting emotional hyperarousal, consistent with nightmares (Perogamvros et al., 2019). Overall, these disorders demonstrate atypical interoceptive processing, which may contribute to core affective and somatic symptoms. This indicates a complex relationship between neural markers of interoception and mental health diagnoses. Understanding the interoceptive disruptions specific to each condition could inform targeted treatments to rebalance the perception of internal bodily states.

The high rates of comorbidities such as depression, anxiety, and sleep disorders in the chronic pain groups raise the possibility that these conditions may influence the interoceptive sensibility found in *Chapter Three*. Future research should control for such comorbidities to clarify whether the relationship between pain impact and interoceptive sensibility is independent of overlapping conditions that also disrupt interoception. Ultimately, an integrative perspective accounting for multifactorial influences is needed to understand interoceptive contributions to chronic pain. Novel techniques such as virtual reality, that target maladaptive interoceptive representations hold promise alongside emerging interoceptive-based interventions. Schoeller et al. (2023) distinguished three levels of

interoceptive technologies: artificial sensations (such as affective touch and hyperventilation tasks to induce artificial panic attacks) that stimulate receptor cells to activate the autonomic system (Di Lernia, Cipresso, et al., 2018; Di Lernia, Riva, et al., 2018; Riva et al., 2017, 2019) and interoceptive illusions (such as false cardiac feedback) that use contextual cues to create false perceptions of inner states (Iodice et al., 2019; Moseley, 2008; Parrotta et al., 2023; Pezzulo et al., 2018). Emotional augmentation combines these techniques with personally significant cues (Schoeller et al., 2019). These techniques complement the emerging immersive approaches for reshaping interoception by targeting maladaptive representations. A systematic review of randomised controlled trials on psychiatric disorders demonstrated the efficacy of interoception-based interventions (Khoury et al., 2018). Further, Feinstein et al. (2018) demonstrate effects of short-term anxiolytic and antidepressant after a single one-hour session of floatation-REST (Reduced Environmental Stimulation Therapy) across a range of anxiety-based and stress-related disorders. A randomised controlled trial (Smith et al., 2021) of a mindfulness-informed interoceptive intervention yielded compelling results in reducing suicidal ideation. Specifically, the authors note that this effect was mediated by the '*body trust'* subscale of the Multidimensional Assessment of Interoceptive Awareness (MAIA; Mehling et al., 2018) - assessed in *Chapter Three* with compelling evidence that trust in one's body is significantly reduced in people with chronic pain conditions than in healthy controls. Integrating findings from emerging interventions that target interoceptive representations indicates promise for novel interoceptive-based treatments to improve outcomes in chronic pain conditions.

The main finding of *Chapter Three* demonstrates a positive association between pain impact and interoceptive sensibility, which initially seems at odds with Damasio's view that "*body-minded minds help save the body*" (Damasio, 1999, p. 143). Damasio's assertion seems to imply that a mind focused on the body benefits the body, that is, it benefits homeostatic regulation. However, our findings are inconsistent with Damasio's idea. It is possible that Damasio refers to minding the body within a normal range, in contrast to the sensitisation and hypervigilance often experienced by people in pain. This would then support the view that higher interoceptive sensibility in people with chronic pain is perhaps a perturbation of the system itself and, by extension, no longer serving the body. Integrating HEP as an objective index of interoception and self-report assessments may clarify whether amplified interoception serves or perturbs the *body-minded mind*.

The unique insight into the cortical representation of bodily signals represented by HEP in *Chapter Two* highlights its potential to elucidate the relationship between pain impact and interoceptive sensibility, as evidenced in *Chapter Three*. Specifically, HEP could be measured under different levels of acute or chronic pain impact. If our prediction holds true that greater pain impact disrupts or diminishes HEP despite heightened self-reported sensibility, it might suggest dysregulation where objective and subjective interoception markers are dissociated. As an objective neural marker, HEP could help clarify the relationship between pain impact and interoceptive sensibility. Clinically, HEP could identify patients with maladaptive amplification (e.g., hypervigilance to pain or bodily signals leading to distress/dysfunction and poorer outcomes) versus adaptive upregulation (e.g., appropriate increase in precision of pain/bodily signals to facilitate coping behaviours, treatment responses, and maintenance of daily functioning) of interoception in chronic pain. Atypical HEP characteristics may identify patients who could benefit from interoception-based interventions such as biofeedback training. As a result, treatment efficacy may be tracked by assessing whether HEP, as an objective metric, effectively normalises alongside interoception-based interventions.

The disrupted brain-body communication observed in clinical conditions may contribute to distorted body perception in chronic pain. This disruption supports the behavioural evidence of impaired interoceptive accuracy in chronic pain populations (Di Lernia et al., 2016, 2020; Duschek et al., 2017; Solcà et al., 2020; Weiss et al., 2014), although there is currently minimal evidence linking HEP to pain perception. In healthy volunteers, Shao et al. (2011) assessed HEP during a cold pressor test, a common method of experimental pain induction in which the participant immerses their hand in cold water to assess physiological responses to the stressor. They reported a reduced HEP amplitude in response to cold pain stimulus but not in response to the no-pain or no-task control conditions. They also distinguished lower subjective pain ratings after five minutes of cold pain were associated with partial recovery of HEP. As demonstrated in *Chapter Two*, interoception has been found to be impaired in people living with CRPS, both behaviourally (via heartbeat counting tasks) and neurally (via HEP), and this was further found to be positively associated with motor impairment and pain duration (Solcà et al., 2020). Similar findings of increased pain-related reports associated with decreased interoceptive accuracy have been found in fibromyalgia (Duschek et al., 2017) and various chronic pain conditions (Di Lernia et al., 2020; Weiss et al., 2014). These findings suggest that reduced HEP and increased pain severity (Shao et al., 2011; Solcà et al., 2020) may indicate an overloaded processing capacity compromising

interoceptive precision, which is interesting when considering the findings of *Chapter Three*: reports of worse pain and mood were associated with higher self-perceived interoception, pointing towards a dysregulation of internal signals.

## 4.7 Concluding Remarks

*Chapter Two* discusses the state of the field of one physiological marker of interoception and presents, for the first time, systematic evidence of physiological interoceptive distinctions across diagnostic groups. This meta-analysis is the first to break down HEP findings by specific diagnostic categories. This reveals important differences between psychiatric, neurological, and cardiovascular conditions.

**Study 1** determined whether, and to what extent, the amplitude of HEP differed between people with a clinically diagnosed condition and a healthy comparison group.

**Study 1** systematically characterised the methodological parameters used to record and analyse HEP to date in the literature.

*Chapter Three* provides a novel investigation of the relationship between pain impact and interoceptive sensibility. Greater pain impact is associated with heightened interoceptive sensibility, affirming interoceptive disruptions in chronic pain disorders. This research provides compelling evidence to suggest that how in tune people with chronic pain think they are with their body is associated with the level of impact their condition has on their life. The relationship between pain impact and body awareness varied across pain conditions, hinting at distinct mechanisms and/or multifactorial relationships.

**Study 2** determined that interoceptive sensibility is associated with pain impact.

**Study 2** characterised the relationship between independent demographic variables, wellbeing, affect, pain, and interoceptive sensibility.

Overall, both chapters provide evidence that interoceptive processing is altered in some chronic conditions, as evidenced by multi-modal markers of interoception. However, the precise nature and impact of these alterations requires further characterisation. These findings match previous evidence that chronic pain and other conditions involve distorted representation of the body, and the findings presented advance the theoretical understanding of the role of interoception in health and disease. These findings also highlight interoception as a potential treatment target for people living with chronic pain.

Interoceptive interventions, such as bodily illusions that alter perceived body size and shape could help normalise disrupted interoception. Research on modulating interoceptive function is rapidly advancing the understanding of interoception in both health and disease. Identifying tailored protocols to restore adaptive predictive coding underlying specific disorders remains an important research priority. Assessing interoception through such modulatory protocols and retraining interoception may improve outcomes that, if successful, may have real-world clinical implications without the common side effects and financial burdens seen today. Multimodal assessment of interoception will clarify the relationship between interventions, neural processes, and symptom outcomes. As such, aligning top-down bodily experiences with bottom-up physiology through interoceptive perturbation assessments and multimodal interoceptive interventions may rebalance the disrupted mind-body mechanisms implicated in chronic pain conditions. However, consensus recommendations on core interoception assessments for research and clinical use are needed to improve consistency across studies and develop such intervention approaches.

In 2021, the National Institute of Health awarded over $18 million to prioritise growing the collective understanding of "*how integrative health approaches may modulate the interoceptive processes and interoceptive clinical outcomes*" (NCCIH, 2021). Building on the aims of this initiative, Chen et al. (2021, p. 13) outlined the following outstanding questions relevant to this thesis:

1. *"What are the effects of modulating interoceptive processes on diseases and disorders of the nervous system?"*
2. *"What are the most effective strategies for developing technologies and approaches to modulate interoceptive processes?"*

In an effort to understand how modulation of interoceptive processes affects clinical conditions, and what approaches can best achieve appropriate modulation (Chen et al., 2021), the current thesis represents an important step toward answering outstanding questions and goals by major research initiatives in this emerging area. Research funding initiatives have recently prioritised work to this end, and the work presented here should make valuable contributions specifically by providing systematic evidence of altered interoceptive processing across multiple chronic conditions using both neural and self-report markers. This thesis highlights the need for multimodal assessments and consistent methodology to advance integrative clinical approaches to interoception. Although further

research is required to directly evaluate interoceptive modulation effects on clinical outcomes, this thesis establishes an empirical foundation and rationale to guide future efforts in this direction.

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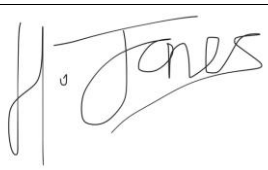
## Appendices

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Appendix 2 – Study 2 Statement of Authorship
Appendix 3 – Study 1 Protocol Registration
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Appendix 5 – Study 2 Protocol Registration
Appendix 7 – Study 2 Checklist of Reporting
Appendix 8 – Study 2 STROBE
Appendix 9 – Study 2 Recruitment Flyer
Appendix 10 – Study 2 Participant Information Sheet
Appendix 12 – Research Dissemination

University of South Australia

# Appendix 1 – Statement of Authorship

| | | |
|---|---|---|
| Title of Paper | Interoception in health and disease: A meta-analytical review of the neurophysiological properties of the heartbeat evoked potential. | |
| Publication Status | ☐ Published<br>☐ Accepted for Publication<br>■ Submitted for Publication<br>☐ Unpublished and Unsubmitted work written in manuscript style | |
| Publication Details<br>Relevant reference details | | |
| **PRINCIPAL AUTHOR** | | |
| Name of Principal Author (Candidate) | Erica M. Wilkinson | |
| Contribution to the Paper Brief description of your work in this publication | Study conception and design, data collection, analysis and interpretation, first full draft, drafting and revision of manuscript, approval of final manuscript | |
| Overall Percentage (%) | 65% | |
| Certification | This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper. | |
| Signature<br>*Signatures will be redacted by the Library at the time of publication* | [redacted] | Date 01/12/2023 |
| **CO-AUTHOR CONTRIBUTIONS** | | |
| By signing the Statement of Authorship, each author certifies that:<br>I. the candidate's stated contribution to the publication is accurate (as detailed above);<br>II. permission is granted for the candidate in include the publication in the thesis; and<br>the sum of all co-author contribution is equal to 100% less the candidate's stated contribution. | | |
| Name of Co-Author 1 | Hannah G. Jones | |
| % Contribution to the Paper | 5% | |

| | | |
|---|---|---|
| Signature<br>*Signatures will be redacted by the Library at the time of publication* |  | Date 04/12/2023 |
| Name of Co-Author 2 | Mark Kohler | |
| % Contribution to the Paper | 5% | |
| Signature<br>*Signatures will be redacted by the Library at the time of publication* | [redacted] | Date 04/12/2023 |
| Name of Co-Author 3 | Lorimer Moseley | |
| % Contribution to the Paper | 10% | |
| Signature<br>*Signatures will be redacted by the Library at the time of publication* | [redacted] | Date 04/12/2023 |
| Name of Co-Author 4 | Carolyn Berryman | |
| % Contribution to the Paper | 15% | |
| Signature<br>*Signatures will be redacted by the Library at the time of publication* | [redacted] | Date 04/12/2023 |

University of South Australia

## Appendix 2 – Statement of Authorship

| | |
|---|---|
| Title of Paper | Minding the body: Interoceptive sensibility is associated with pain impact in people with chronic pain disorders. |
| Publication Status | ☐ Published<br>☐ Accepted for Publication<br>■ Submitted for Publication<br>☐ Unpublished and Unsubmitted work written in manuscript style |
| Publication Details<br>Relevant reference details | |
| **PRINCIPAL AUTHOR** | |
| Name of Principal Author (Candidate) | Erica M. Wilkinson |
| Contribution to the Paper<br>Brief description of your work in this publication | Study conception and design recruitment, data collection, analysis and interpretation, first full draft, drafting and revision of manuscript, approval of final manuscript |
| Overall Percentage (%) | 70% |
| Certification | This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper. |
| Signature<br>*Signatures will be redacted by the Library at the time of publication* | [redacted] Date 01/12/2023 |
| **CO-AUTHOR CONTRIBUTIONS** | |
| By signing the Statement of Authorship, each author certifies that:<br>III. the candidate's stated contribution to the publication is accurate (as detailed above);<br>IV. permission is granted for the candidate in include the publication in the thesis; and<br>V. the sum of all co-author contribution is equal to 100% less the candidate's stated contribution. | |
| Name of Co-Author 1 | Mark Kohler |
| % Contribution to the Paper | 10% |

| | | |
|---|---|---|
| Signature<br>*Signatures will be redacted by the Library at the time of publication* |  | Date 04/12/2023 |
| Name of Co-Author 2 | Lorimer Moseley | |
| % Contribution to the Paper | 10% | |
| Signature<br>*Signatures will be redacted by the Library at the time of publication* |  | Date 04/12/2023 |
| Name of Co-Author 3 | Carolyn Berryman | |
| % Contribution to the Paper | 10% | |
| Signature<br>*Signatures will be redacted by the Library at the time of publication* |  | Date 04/12/2023 |

## Appendix 3 – Study 1 Protocol Registration

# The neurophysiological properties of the heartbeat evoked potential in health and disease: A systematic review protocol

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[2] IIMPACT in Health, School of Health Science, University of South Australia, Australia [3]Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide [4]Adelaide Brain and Cognitive Development laboratory, School of Psychology, Faculty of Health and Medical Sciences, University of Adelaide
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## Abstract

Background: The heartbeat evoked potential (HEP) reflects the cortical processing of the heartbeat and is considered a marker of interoceptive function. Broadly speaking, greater HEP amplitude is thought to reflect better interoceptive performance. Interoceptive dysfunction has been implicated in various psychopathologies and clinical conditions, but significant gaps exist in our understanding of the current evidence concerning these implications.

Objective: To provide a protocol for a systematic review on the neurophysiological properties underlying HEPs in clinical conditions and healthy controls.

Methods: The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) will be used as a guideline for this protocol.

Results: The systematic review will commence after registration of this protocol on Open Science Framework, where it will be locked, and date stamped.

Conclusions: Given the developing field of research regarding HEPs within various populations, this systematic review will provide a comprehensive synthesis of the neurophysiological properties of HEPs in various groups. The literature review will identify the strengths and limitations of the studies that have provided primary data on HEPs, and by extension, identify any existing gaps in the literature to inform further research on HEP as a useful biomarker of interoception.

Keywords: heartbeat evoked potential, event related potentials, cardiac-afferent signal, evoked potentials (MeSH), heart rate (MeSH), chronic pain, depression, anxiety, PTSD, fibromyalgia, biomarker.

## Introduction

The heartbeat evoked potential (HEP) is an objective index of the cortical processing of the heartbeat (Schandry, Sparrer, & Weitkunat, 1986). The HEP *is* thought to be produced via detection of changes in blood pressure within the aorta and the carotid arteries, that effectively encode cardiac cycle oscillations and fluctuations of both timing and strength of heart beats. Ascending projections continuously update brain-held 'maps' of cardiac activity. Thus, the HEP has been theorised as an index of cardiac interoception (Park & Blanke, 2019; Silvani et al., 2016).

## Methods

### Data Sources

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISNIA-P) will be used as a guideline for this protocol (*Appendix 1*). A systematic searcl1 of the following electronic databases will be performed from inception to (exact date of final searcl1es nm): MEDLINE (OvidSP), Cochrane (Cochrane Library), SCOPUS (Elsevier), Embase (OvidSP), EmCare (OvidSP), PsychINFO (OvidSP), and Web of Science (Clarivate Analytics) to retrieve articles relating to the heartbeat evoked potential (see *Appendix 2* for full search strategy). A combination of subject headings and keywords relating to the heartbeat evoked potential will be used. Following duplicate removal, two independent reviewers will evaluate the retrieved titles and abstracts for inclusion, with any discrepancies being resolved by discussion or consultation with a third reviewer. Upon completion of this process, full texts of tl1e remaining articles will be retrieved. Given the review aims to capture the neurophysiological properties of the heartbeat evoked potential in both healthy and clinical populations, the databases were selected based on how well they reflect these populations. To capture any missed articles, all reference lists of included studies will be manually checked.

### Eligibility Criteria

A sample eligibility form will be produced and piloted before commencing the search. A PICO framework will be used to define the research question and strategy in the following way:

**Population:** Adult (>18) human subjects with a disease. Studies that do not include a standardised measure or professional diagnosis will be excluded.

**Intervention:** Interoceptive task performance as specified by the author.

**Comparison:** A diagnosed group in comparison to a healthy state or a healthy control group.

**Outcome:** To be included, the study will be required to include a HEP response (primary outcome). The review will also explore secondary outcomes including interoceptive tasks and the relationship between the HEP and task performance. Given the variability in reported HEP response, an outcome will be considered to be a response of HEP when the original study authors define *it* as such.

#### Inclusion Criteria

- Human adults
- Over 18 years old
- Any sex and/ or gender

- Any condition (healthy clinical, sub-clinical diagnoses or comorbid diagnoses).
- Any language or setting

Exclusion Criteria

- Animal studies
- Grey literature and secondary data (e.g., systematic reviews or meta-analyses)
- Book chapters

## Data Collection and Analysis

Data extraction

Studies that are identified by the systematic search will be uploaded to Endnote (Clarivate Analytics, Philadelphia, PA, USA) where duplicates will be removed before uploading all results to Covidence (Covidence.org) to be screened by title and abstract by two independent reviewers. Data extraction will be completed by two independent reviewers using a customised, piloted data extraction form. Any disagreements will be resolved by discussion, and if necessary, through consultation with a third reviewer. Results will then be compared for accuracy. If any data are missing, authors will be requested for data a maximum of three times. If there is no satisfactory retrieval of data at this point, the data will be considered irretrievable.

The following information will be extracted:

- Group-specific data
    - Type of disease state/ clinical condition and healthy control
    - Sample size in each group
    - Gender
    - Age (mean and standard deviation)
    - Reported group averages, range, deviations from averages
- Process of recruitment
- EEG setup
- ECG set up
- HEP measurement protocol
- HEP characteristic information
- HEP modulators
- Stimuli used
- Task used
    - Interoceptive task
        - Subjective (self-report or Interoceptive Accuracy)
        - Behavioural (Interoceptive Accuracy measure)
    - Other tasks (attention vs. distraction, interoception vs. exteroception, task vs. baseline)
- Group specific outcomes on HEP and behavioural measures
    - Mean and standard deviation for all spatial and temporal parameters of the HEP reported by the primary article, for each group.
    - Z-scores,
    - Mean differences
- Statistical method data
    - Variables used to match groups
    - Covariates used in analysis

- Secondary outcomes if reported
    - Heartbeat counting task
    - Heartbeat discrimination task
    - Spearman's or Pearson's correlations between **HEP** parameter and task parameter

### Risk of Bias assessment

A Risk of Bias of individual studies will be employed to assess the potential risk of bias and the quality of the included studies. A modified version of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist (www.strobe-statement.org) for cross-sectional studies will be used to assess Risk of Bias. The checklist will be adapted to critically appraise each included paper based on specific criteria relevant to the review objectives. This will be carried out by two reviewers independently. Disagreements will be resolved tl1rough discussion between reviewers, and if still not resolved, through consultation witl1 a third reviewer. In the event of a randomised controlled trial being included in this review, tl1e Cochrane Collaborative Risk of Bias Tool will be used. The quality of the studies will be included in a table of tl1e publication.

### Assessment of heterogeneity

Statistical heterogeneity will be assessed using Pearson's chi-square *(X2)* test for homogeneity of variance and Higgins and Thompson's *I2* statistic. In accordance with the Cochrane criteria, heterogeneity will be deemed statistically significant on the basis of X2 p<.10 and substantial heterogeneity when I2 > 60% (Higgins & Green, 2011).

### Data pooling

If the data extraction process identifies a clear separation in methods reported, included studies will be pooled. However, this decision will be guided by the data. If pooled coefficients are similar (i.e. if the mean correlation is within 1 SD), a meta-analysis will be performed on tl1e dataset using a random effects model in Review Manager (RevMan, v. 5.3). The effect estimates will be presented as forest plots. For each group, the mean and pooled standard deviations of the outcome data will be used to calculate tl1e standardised mean difference (Hedge's g: SMD). Study characteristics will be examined using descriptive statistics. Interpretation of effect sizes will be based on Cohen's *d* where 0.2, 0.5, and 2:0.8 will be considered small, moderate, and large effect sizes, respectively (Cohen, 1992). If the data are sufficient, post hoc sensitivity analyses will be completed.

This systematic review will commence after registration of this protocol on Open Science Framework, where it will be locked and date stamped. A narrative synthesis will be included of the physiological properties of HEPs and will be supported by a table of the main results. Studies will be grouped by type of diagnostic condition for data synthesis. This will both summarise and highlight any gaps in tl1e literature in which further research is needed.

## Acknowledgements

The authors would like to acknowledge the guidance and careful review of the search strategy by the academic Librarian, SM. The primary reviewer (E. Wilkinson) is supported by the Commonwealth Government fee waiver scholarship as a postgraduate student at the University of South Australia. GLM is supported by a Leadership Investigator grant from the National Health & Medical Research Council of Australia. CB *is* supported by an Early Career Research Fellowship from the National Health & Medical Research Cow1eil of Australia.

## Contributions

Conception & design: EMW, CB, MK, GLM Search strategy: EMW, HJ
Methods: EMW, CB, HJ, MK, GLM
Guarantor: GLM

## Conflicts of Interest

None declared.

## Abbreviations

HEP: heartbeat evoked potential
EEG: electroencephalography ECG: electrocardiography
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses MeSH: Medical Subject Headings

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Schandry, R., Sparrer, B., & Weitkunat, R. (1986). From the heart to the brain: A study of heartbeat contingent scalp potentials. *International journal of Neuroscience,* 30(4), 261-275 doi: 10.3109/ 00207458608985677

Silvani, A., Calandra-Buonaura, G., Dampney, R. A., & Cortelli, **P.** (2016). Brain-heart interactions: physiology and clinical implications. *Philosophical Transactions A Royal Society, 314(2067)* :20150181 doi: 10.1098/rsta.2015.0181

**Appendix 1 - Table displaying the PRISMA-P 2015 Checklist:** table adapted from Table 2 in Shamseer, L. *et al.* (2015) 'Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation', *BMJ*, 349, p. g7647. doi: 10.1136/bmj.g7647.

| Section and Topic | # | Checklist Item | Information reported? | | Page Number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| Administrative information | | | | | |
| Title: identification | 1a | Identify the report as a protocol of a systematic review | | | 1 |
| Title: Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | | | |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | | | |
| Authors: Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | | | 13 |
| Authors: Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | | | 6 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | | | |
| Support: Sources | 5a | Indicate sources of financial or other support for the review | | | 6 |
| Support: Sponsor | 5b | Provide name for the review funder and/or sponsor | | | 6 |
| Support: Role of Sponsor or Funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | | | 6 |
| Introduction | | | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | | | 3 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | | | 3 |
| Methods | | | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | | | 3,4 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | | | 4 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | | | 10 |
| Study records: data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | | | 4 |
| Study records: selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | | | 4 |
| Study records: data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | | | 4 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | | | 4,5 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | | | 4,5 |

| | | | | | |
|---|---|---|---|---|---|
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | | | 5 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | | | 5 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ) | | | 5 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | | | 5 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | | | |
| Meta bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | | | 5 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | | | 5 |

## Appendix 2 – Search Strategy

### Medline

1. Evoked Potentials/
2. Event-Related Potentials/
3. 1 or 2
4. Heart Rate/
5. 3 and 4
6. (Cardiac-afferent signal* or cardio-afferent signal* or Heart?beat-evoked potential? or heart?rate-evoked potential? or heart? beat?-evoked potential? or heart? Rate?-evoked potential? or Heart?beat-evoked response? or heart?rate-evoked response? or heart?beat evoked potential* or heart? beat?-evoked response? or heart? Rate?-evoked response?).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7. ((Heart beat* or Heart?beat* or Heart rate* or Heart?rate or cardiac or cardio) adj3 (evoked potential? or evoked response? or event-related potential? or event related potential? or Evoked brain? Potential? or afferent signal* or scalp potential? or "Neural response? to")).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. 5 or 6 or 7
9. (amplitude? or latenc* or latent or wave* or magnitud*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 8 and 9
11. limit 10 to humans
12. limit 10 to animals
13. 10 not 12
14. 11 or 13

### Scopus

( TITLE-ABS-KEY ( amplitude* OR latenc* OR latent OR wave* OR magnitud* ) ) AND ( ( TITLE-ABS-KEY ( "Cardiac-afferent signal*" OR "cardio-afferent signal*" OR "Heart-beat-evoked potential*" OR "Heartbeat-evoked potential*" OR "heart-rate-evoked potential*" OR "heartrate-evoked potential*" OR "heart* beat-evoked potential*" OR "heart* beatevoked potential*" OR "heart* Rate-evoked potential*" OR "heart* Rateevoked potential*" OR "Heart-beat-evoked response*" OR "Heartbeat-evoked response*" OR "heart-rate-evoked response*" OR "heartrate-evoked response*" OR "heart-beat evoked potential*" OR "heartbeat evoked potential*" OR "heart* beat-evoked response*" OR "heart* Rate-evoked response*" OR "heart* Rateevoked response*" ) ) OR ( TITLE-ABS-KEY ( ( "Heart

beat*" OR heartbeat* OR heart-beat OR "Heart rate*" OR heart-rate OR heartrate OR cardiac OR cardio ) W/3 ( "evoked potential" OR "evoked potentials" OR "evoked response*" OR "event-related potential" OR "event-related potentials" OR "event related potential" OR "event related potentials" OR "Evoked brain* Potential" OR "evoked brain* potentials" OR "afferent signal*" OR "scalp potential" OR "scalp potentials" OR "Neural response to" OR "Neural response to" ) ) ) )

## PsycINFO

1. Evoked Potentials/
2. Heart Rate/
3. 1 and 2
4. (Cardiac-afferent signal* or cardio-afferent signal* or Heart?beat-evoked potential? or heart?rate-evoked potential? or heart? beat?-evoked potential? or heart? Rate?-evoked potential? or Heart?beat-evoked response? or heart?rate-evoked response? or heart?beat evoked potential* or heart? beat?-evoked response? or heart? Rate?-evoked response?).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]
5. ((Heart beat* or Heart?beat* or Heart rate* or Heart?rate or cardiac or cardio) adj3 (evoked potential? or evoked response? or event-related potential? or event related potential? or Evoked brain? Potential? or afferent signal* or scalp potential? or "Neural response? to")).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]
6. 3 or 4 or 5
7. (amplitude? or latenc* or latent or wave* or magnitud*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]
8. 6 and 7

## Embase

1. Evoked response/
2. Event Related Potential/
3. 1 or 2
4. Heart Rate/
5. 3 and 4
6. (Cardiac-afferent signal* or cardio-afferent signal* or Heart?beat-evoked potential? or heart?rate-evoked potential? or heart? beat?-evoked potential? or heart? Rate?-evoked potential? or Heart?beat-evoked response? or heart?rate-evoked response? or heart?beat evoked potential* or heart? beat?-evoked response? or heart? Rate?-evoked response?).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. ((Heart beat* or Heart?beat* or Heart rate* or Heart?rate or cardiac or cardio) adj3 (evoked potential? or evoked response? or event-related potential? or event related potential? or Evoked brain? Potential? or afferent signal* or scalp potential? or "Neural response? to")).mp. [mp=title, abstract, heading word, drug trade

name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

8. 5 or 6 or 7

9. (amplitude? or latenc* or latent or wave* or magnitud*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

10. 8 and 9

11. limit 10 to humans

12. limit 10 to animals

13. 10 not 12

14. 11 or 13

## Emcare

1. Evoked response/

2. Event Related Potential/

3. 1 or 2

4. Heart Rate/

5. 3 and 4

6. (Cardiac-afferent signal* or cardio-afferent signal* or Heart?beat-evoked potential? or heart?rate-evoked potential? or heart? beat?-evoked potential? or heart? Rate?-evoked potential? or Heart?beat-evoked response? or heart?rate-evoked response? or heart?beat evoked potential* or heart? beat?-evoked response? or heart? Rate?-evoked response?).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

7. ((Heart beat* or Heart?beat* or Heart rate* or Heart?rate or cardiac or cardio) adj3 (evoked potential? or evoked response? or event-related potential? or event related potential? or Evoked brain? Potential? or afferent signal* or scalp potential? or "Neural response? to")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

8. 5 or 6 or 7

9. (amplitude? or latenc* or latent or wave* or magnitud*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

10. 8 and 9

11. limit 10 to humans

12. limit 10 to animals

13. 10 not 12

14. 11 or 13

## Cochrane

#1 MeSH descriptor: [Evoked Potentials]

#2 MeSH descriptor: [Heart Rate]

#3 #1 and #2

#4 (cardiac-afferent NEXT signal*) or (cardio-afferent NEXT signal*) or (Heart-beat-evoked NEXT potential?) or (Heartbeat-evoked NEXT potential?) or (heartrate-evoked NEXT potential?) or (heart-rate-evoked NEXT potential?) or (heart? NEXT "beat-evoked potential") or (heart? NEXT "beat-evoked potentials") or (heart? NEXT "beatevoked potential") or (heart? NEXT "beatevoked potentials") or (heart? NEXT "Rateevoked potential") or (heart? NEXT "Rateevoked potentials") or (heart? NEXT "Rate-evoked potential") or (heart? NEXT "Rate-evoked potentials") or (Heart-beat-evoked NEXT response?) Or (Heartbeat-evoked NEXT response?) or (heartrate-evoked NEXT response?) or (heart-rate-evoked NEXT response?) or ("heartbeat evoked" NEXT potential*) or ("heart-beat evoked" NEXT potential*) or ("heart beatevoked" NEXT response?) or ("hearts beatevoked" NEXT response?) Or ("hearts beat-evoked" NEXT response?) or ("heart beatevoked" NEXT response?) Or (heart? NEXT "beat-evoked response") or (heart? NEXT "beat-evoked responses")

#5 ("Heart beat" or "heart beats" or Heart-beat* or heartbeat* or "Heart rate" or "heart rates" or Heart-rate* or heartrate* or cardiac or cardio) NEAR/3 ("evoked potential" or "evoked potentials" or "evoked response" or "evoked responses" or "event-related potential" or "event-related potentials" or "event related potential" or "event related potentials" or "Evoked brain Potential" or "evoked brains potential" or "evoked brain potentials" or "evoked brains potentials" or "afferent signal" or "afferent signals" or "afferent signalling" or "scalp potential" or "scalp potentials" or "Neural response to" or "neural responses to")

#6#3 or #4 or #5

**Investigator details:**

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## Appendix 4 – Study 1 Protocol Amendment

| Date | Authors | Amendment | Rationale |
|---|---|---|---|
| **14062023** | EMW | Insert “scalp-level” HEP response to Table 1 | To clarify the exclusion of electrocortical-level HEP |
| **19112022** | EMW | Clarify PRISMA item 10a for multiple outcomes reported | The team decided a priori that the largest effect size would be used but this was not included in the protocol |
| **03112022** | EMW | Re-run searches | To capture the most up to date publications |
| **28072022** | EMW | Classification Justification for Subgroup Allocation | To provide justification for the subjectivity of subgroup classification |
| **22062022** | EMW | Removed “The review will also explore secondary outcomes including interoceptive tasks and the relationship between the task and physiological response.” From protocol | Beyond the scope of this review |
| **07092021** | EMW | Added Meta-analysis appraisal questions | Based on recommendation from literature |
| **22032021** | EMW | Updated analysis plan to account for nonindependence | Component of a multilevel model to account for |
| **22032021** | EMW | Changed from CMA to using R with Metafor package | Unable to perform a multilevel model using CMA |
| **18102019** | EMW | Changed from Endnote to Zotero | Better integration |

## Appendix 5 – Study 2 Protocol Registration

Minding the body - Interoceptive sensibility is associated with pain impact in people with chronic pain disorders

Contributors: Erica Wilkinson

Date created: 2023-11-06 03:55 PM | Last Updated: 2023-11-06 04:15 PM

Category: Project

License: CC0 1.0 Universal

Description:

We aimed to investigate whether and to what extent body awareness and autonomic reactivity differed between three persistent pain states - fibromyalgia (FM), complex regional pain syndrome (CRPS) and chronic musculoskeletal pain (CMP) - and healthy controls. Our secondary aim was to investigate the relationship between self-report measures of body awareness, and autonomic reactivity and pain.

Analysis Plan

The primary outcome we are interested in is the difference between the groups on the 3 domains of the body perception questionnaire (awareness, subdiaphragmatic, and supradiaphragmatic). The secondary outcome is whether any of these values are correlated with either severity or interference scores of the brief pain index. We will use a linear model for each domain (awareness, subdiaphragmatic, supradiaphragmatic) outcome (3 linear models) with fixed factors Age, Gender, DASS overall score and no random factors (because there is no interindividual variance with one score per person, so we are unable to model residuals). We will calculate the Pearson correlation coefficient to investigate the association between our BPQ outcomes and bpi interference and severity.

Analysis Deviation from Protocol (Forked osf.io/ns2d5):

Aim 1: Relationship between pain impact and interoceptive sensibility

Pearson correlation analysis was conducted to determine the relationship between pain impact (F/SIQ-R) and interoceptive sensibility (BPQ-Awareness) across groups. Standardised beta coefficients (β) were determined for group-specific correlations.

Aim 2: Characterisation of the dataset and the influence of independent variables on interoceptive sensibility

Linear regression analysis was conducted to investigate whether interoceptive sensibility differed across conditions. The model assumptions were evaluated using the performance R package. Group, age, total DASS score, and BPI Interference variables were included as fixed factors in the

model. To assess the model fit, the full model was compared to a reduced model in which DASS and BPI were not included (see *Supplementary Table 1*). Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to determine model fit. The final model was selected on the basis of a model with lower AIC and BIC metrics. We compared the model fit and performed post hoc comparisons using pairwise t-tests.

Next, a Pearson correlation was conducted to determine the relationship between all interoceptive sensibility measures (BPQ-Awareness and MAIA) and all pain measures (BPI, PCS, CSI, DASS, and PSQI) across the total sample (n = 260). Correlation coefficients (*r*) and significance values (*p*) were reported in the overall linear correlation, and p-values were adjusted for multiple correlations using the Holm-Bonferroni method. The mean ± standard deviation values are reported, unless otherwise stated. Statistical significance was set at $p < .05$.

Appendix 6 – Study 2 Checklist for Reporting Results of Internet E-Surveys (CHERRIES)

| Checklist Item | Explanation | Page Number |
|---|---|---|
| **Describe survey design** | Describe target population, sample frame. Is the sample a convenience sample? (In "open" surveys this is most likely.) | Methods: Participants |
| **IRB approval** | Mention whether the study has been approved by an IRB. | Methods: Procedure |
| **Informed consent** | Describe the informed consent process. Where were the participants told the length of time of the survey, which data were stored and where and for how long, who the investigator was, and the purpose of the study? | Methods: Procedure |
| **Data protection** | If any personal information was collected or stored, describe what mechanisms were used to protect unauthorized access. | Appendix 10 |
| **Development and testing** | State how the survey was developed, including whether the usability and technical functionality of the electronic questionnaire had been tested before fielding the questionnaire. | Methods: piloted each questionnaire |
| **Open survey versus closed survey** | An "open survey" is a survey open for each visitor of a site, while a closed survey is only open to a sample which the investigator knows (password-protected survey). | Methods: open survey |
| **Contact mode** | Indicate whether or not the initial contact with the potential participants was made on the Internet. (Investigators may also send out questionnaires by mail and allow for Web-based data entry.) | Methods: internet |
| **Advertising the survey** | How/where was the survey announced or advertised? Some examples are offline media (newspapers), or online (mailing lists – If yes, which ones?) or banner ads (Where were these banner ads posted and what did they look like?). It is important to know the wording of the announcement as it will heavily influence who chooses to participate. Ideally the survey announcement should be published as an appendix. | Methods: Procedure; Appendix 9 Recruitment Poster |

| | | |
|---|---|---|
| **Web/E-mail** | State the type of e-survey (eg, one posted on a Web site, or one sent out through e-mail). If it is an e-mail survey, were the responses entered manually into a database, or was there an automatic method for capturing responses? | Qualtrics; Results exported automatically. |
| **Context** | Describe the Web site (for mailing list/newsgroup) in which the survey was posted. What is the Web site about, who is visiting it, what are visitors normally looking for? Discuss to what degree the content of the Web site could pre-select the sample or influence the results. For example, a survey about vaccination on a anti- immunization Web site will have different results from a Web survey conducted on a government Web site | Methods: Qualtrics Results entered automatically into database |
| **Mandatory/voluntary** | Was it a mandatory survey to be filled in by every visitor who wanted to enter the Web site, or was it a voluntary survey? | Methods: Voluntary |
| **Incentives** | Were any incentives offered (eg, monetary, prizes, or non-monetary incentives such as an offer to provide the survey results)? | Methods: Incentive 1 in 10 $40 visa |
| **Time/Date** | In what timeframe were the data collected? | |
| **Randomization of items or questionnaires** | To prevent biases items can be randomized or alternated. | Methods: Randomised order of scales |
| **Adaptive questioning** | Use adaptive questioning (certain items, or only conditionally displayed based on responses to other items) to reduce number and complexity of the questions. | Yes |
| **Number of Items** | What was the number of questionnaire items per page? The number of items is an important factor for the completion rate. | |
| **Number of screens (pages)** | Over how many pages was the questionnaire distributed? The number of items is an important factor for the completion rate. | |
| **Completeness check** | It is technically possible to do consistency or completeness checks before the questionnaire is submitted. Was this done, and if "yes", how (usually JAVAScript)? An alternative is to check for completeness after the questionnaire has been submitted (and highlight mandatory items). If this has been done, it should be reported. All items should provide a non-response option such as "not applicable" or "rather not say", and selection of one response option should be enforced. | Results |
| **Review step** | State whether respondents were able to review and change their answers (eg, through a Back button or a Review step which | Yes: Back button |

| | | |
|---|---|---|
| | displays a summary of the responses and asks the respondents if they are correct). | |
| **Unique site visitor** | If you provide view rates or participation rates, you need to define how you determined a unique visitor. There are different techniques available, based on IP addresses or cookies or both. | IP |
| **View rate (Ratio of unique survey visitors/unique site visitors)** | Requires counting unique visitors to the first page of the survey, divided by the number of unique site visitors (not page views!). It is not unusual to have view rates of less than 0.1 % if the survey is voluntary. | NA |
| **Participation rate (Ratio of unique visitors who agreed to participate/unique first survey page visitors)** | Count the unique number of people who filled in the first survey page (or agreed to participate, for example by checking a checkbox), divided by visitors who visit the first page of the survey (or the informed consents page, if present). This can also be called "recruitment" rate. | NA |
| **Completion rate (Ratio of users who finished the survey/users who agreed to participate)** | The number of people submitting the last questionnaire page, divided by the number of people who agreed to participate (or submitted the first survey page). This is only relevant if there is a separate "informed consent" page or if the survey goes over several pages. This is a measure for attrition. Note that "completion" can involve leaving questionnaire items blank. This is not a measure for how completely questionnaires were filled in. (If you need a measure for this, use the word "completeness rate".) | Results |
| **Cookies used** | Indicate whether cookies were used to assign a unique user identifier to each client computer. If so, mention the page on which the cookie was set and read, and how long the cookie was valid. Were duplicate entries avoided by preventing users access to the survey twice; or were duplicate database entries having the same user ID eliminated before analysis? In the latter case, which entries were kept for analysis (eg, the first entry or the most recent)? | Duplicate entries were removed. The entry that was most complete was retained. |
| **IP check** | Indicate whether the IP address of the client computer was used to identify potential duplicate entries from the same user. If so, mention the period of time for which no two entries from the same IP address were allowed (eg, 24 hours). Were duplicate entries avoided by preventing users with the same IP address access to the survey twice; or were duplicate database entries having the same IP address within a given period of time eliminated before analysis? If the latter, which entries were kept for analysis (eg, the first entry or the most recent)? | Yes |
| **Log file analysis** | Indicate whether other techniques to analyze the log file for identification of multiple entries were used. If so, please describe. | Progress rate |

| | | |
|---|---|---|
| **Registration** | In “closed” (non-open) surveys, users need to login first and it is easier to prevent duplicate entries from the same user. Describe how this was done. For example, was the survey never displayed a second time once the user had filled it in, or was the username stored together with the survey results and later eliminated? If the latter, which entries were kept for analysis (eg, the first entry or the most recent)? | NA |
| **Handling of incomplete questionnaires** | Were only completed questionnaires analyzed? Were questionnaires which terminated early (where, for example, users did not go through all questionnaire pages) also analyzed? | Yes;<br>Yes if over 70% complete |
| **Questionnaires submitted with an atypical timestamp** | Some investigators may measure the time people needed to fill in a questionnaire and exclude questionnaires that were submitted too soon. Specify the timeframe that was used as a cut-off point, and describe how this point was determined. | Yes |
| **Statistical correction** | Indicate whether any methods such as weighting of items or propensity scores have been used to adjust for the non- representative sample; if so, please describe the methods. | No |

This checklist has been modified from Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res. 2004 Sep 29;6(3):e34 [erratum in J Med Internet Res. 2012; 14(1): e8.]. Article available at https://www.jmir.org/2004/3/e34/; erratum available https://www.jmir.org/2012/1/e8/. Copyright ©Gunther Eysenbach. Originally published in the Journal of Medical Internet Research, 29.9.2004 and 04.01.2012.

This is an open-access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/2.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in the Journal of Medical Internet Research, is properly cited.

## Appendix 7 – Study 2 STROBE

| | | Reporting Item | Page Number |
|---|---|---|---|
| | **Title and abstract** | | |
| **1a** | Title | Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| **1b** | Abstract | Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| | **Introduction** | | |
| **2** | Background / rationale | Explain the scientific background and rationale for the investigation being reported | 3 |
| **3** | Objectives | State specific objectives, including any prespecified hypotheses | 4 |
| | **Methods** | | |
| **4** | Study design | Present key elements of study design early in the paper | 4 |
| **5** | Setting | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7 |
| **6a** | Eligibility criteria | Give the eligibility criteria, and the sources and methods of selection of participants. | 7 |
| **7** | | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | |
| **8** | Data sources / measurement | For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable. | 4-7 |
| **9** | Bias | Describe any efforts to address potential sources of bias | 7 |
| **10** | Study size | Explain how the study size was arrived at | 4 |
| **11** | Quantitative variables | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 9 |
| **12a** | Statistical methods | Describe all statistical methods, including those used to control for confounding | 9 |
| **12b** | Statistical methods | Describe any methods used to examine subgroups and interactions | 9 |
| **12c** | Statistical methods | Explain how missing data were addressed | 10 |
| **12d** | Statistical methods | If applicable, describe analytical methods taking account of sampling strategy | NA |
| **12e** | Statistical methods | Describe any sensitivity analyses | 12 |
| | **Results** | | |
| **13a** | Participants | Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable. | 8, 10 |
| **13b** | Participants | Give reasons for non-participation at each stage | 8, 10 |
| **13c** | Participants | Consider use of a flow diagram | 8 |

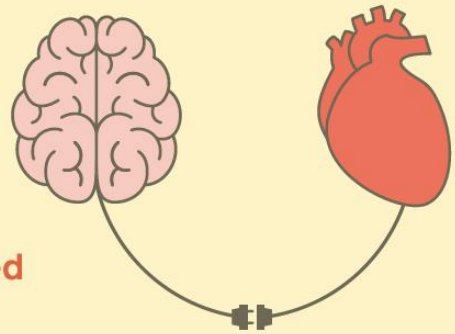
| | | | |
|---|---|---|---|
| **14a** | Descriptive data | Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable. | 11-17 |
| **14b** | Descriptive data | Indicate number of participants with missing data for each variable of interest | NA |
| **15** | Outcome data | Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable. | NA |
| **16a** | Main results | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 10 |
| **16b** | Main results | Report category boundaries when continuous variables were categorized | NA |
| **16c** | Main results | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| **17** | Other analyses | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | 12-21 |
| | **Discussion** | | |
| **18** | Key results | Summarise key results with reference to study objectives | 21-25 |
| **19** | Limitations | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. | 24 |
| **20** | Interpretation | Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. | 24-25 |
| **21** | Generalisability | Discuss the generalisability (external validity) of the study results | 24-25 |
| | **Other Information** | | |
| **22** | Funding | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 26 |

Appendix 8 – Study 2 Recruitment Flyer

University of South Australia

# Research Participants Wanted

The heart of the matter: Investigating interoception in people with **fibromyalgia**.



**We are looking for right handed people with fibromyalgia and healthy people aged between 18 and 85 years**
to participate in a study investigating how the heart and brain work in people with fibromyalgia.

**Location: UniSA City East (corner of North Terrace and Frome Road)**
**Duration: 2h and 10m**
**Compensation: $40 VISA**

To find out more, scan the QR code or take a slip below!

This project has been approved by the University of South Australia's Human Research Ethics Committee. Participants or third parties who wish to lodge a complaint about either the study or the way it is being conducted should contact the Executive Officer of UniSA HREC in the first instance, email: humanethics@unisa.edu.au or tel: 8302 3118.

Interoception in Fibromyalgia
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0419151813

# Appendix 9 – Study 2 Participant Information Sheet



University of South Australia

## Informed Consent and Demographics

**Participant Information Sheet**

You are invited to participate in a project investigating how we perceive our bodies. This project is being conducted by the Body in Mind Research Group within the IIMPACT Research Group at the University of South Australia. It will involve you completing an online survey which will take approximately 30 minutes to complete. The purpose of the research is to understand how different cognitive factors can predict the ability to perceive internal bodily signals, and by extension, how this differs in people with a clinical condition. Research outcomes could provide some new methods to treat fibromyalgia where bodily perception is affected.

In order to be eligible, you must satisfy the following two criteria:

- You are aged between 18 – 85
- You live in Australia

Your participation is completely voluntary, and you may withdraw your consent at any time without affecting your position now or in the future. If you withdraw your consent prior to testing being completed, your data will not be included in the analysis / publication of the study. Please be reassured that all records containing personal information (i.e., the consent form) will remain confidential and no information which could lead to the identification of any participant will be released unless required by law.

Data will be securely stored electronically on a computer at the University of South Australia indefinitely after project completion / publication of the results and will only be accessed by study investigators. Results will be stored in a coded (re-identifiable)format until publication, at which time the codes allowing for re-identification will be deleted. Please note that non-identifiable data collected in this project may be used as comparative data in future projects, for which ethics approval will be sought. Importantly, the anonymised form will ensure that no inference can be drawn from the data about your identity.

If you are happy to participate in this research, please see the consent form below. As compensation for your time and effort, we will automatically add your email address to go in the draw to win one of 10 $40 EFTPOS VISA cards, which you will be drawn upon completion of the study.

If you would like to be informed about the results of this study, please provide the researcher with your email address. We will then email you a summary of the study results once the project has been completed.

This project has been approved by the University of South Australia's Human Research Ethics Committee (protocol #203294). If you have any ethical concerns about the project or questions about your rights as a participant please contact the Ethics Committee humanethics@unisa.edu.au.

Yours sincerely,
Professor Lorimer Moseley, Principal Investigator and Supervisor.
Email: lorimer.moseley@unisa.edu.au

By selecting "I agree" below, you agree that:

- You have read and understood the participant information sheet
- Questions about your participation in this study have been answered satisfactorily
- You are aware of the potential risks (if any)
- You give the researcher permission to use the data from this survey for subsequent and future research for which ethics approval will be obtained
- You give the researchers permission to keep the de-identified data for an indefinite period so that it may be used as comparative data in future projects, such as in secondary analyses, for which ethics approval will be sought
- You are taking part in this research study voluntarily (without coercion) and consent to participate in this study is by virtue of choosing to complete the survey
- You are aged between 18 - 85
- You are a native speaker of English
- You agree to be contacted about participation in future studies understanding that participation is on a purely voluntary basis

I agree
I do not agree, exit the survey

# Appendix 10 – Online Survey

What is your age?

Age:

What is your gender?

- ○ Male
- ○ Female
- ○ [ ] Other, please specify

Where were you born?

[ ]

Are you left or right handed?

- ○ Left
- ○ Right
- ○ Ambidextrous

Are you of Aboriginal or Torres Strait Islander descent?

- ○ Yes
- ○ No
- ○ Prefer not to say

## Survey Outline

In this survey you will be asked to complete multiple sections, please read the outlines below before you start. We don't expect that any of the questions will cause you distress, but if you do become upset or feel uncomfortable during the survey and wish to stop, please remember that participation in the study is voluntary and that you may stop at any time.

**Informed Consent -** This section provides you with information about the study, what is required of you if you choose to participate, and any potential risks to you. You are then able to decide whether you consent to this study or not. If you choose to take part, you will first be asked some questions about your general life.

**Demographics -** This section specifically asks you about your experiences.

**Symptom Impact Questionnaire -** This scale asks you to indicate how much you feel that fibromyalgia has impacted your ability to do different activities over the past week.

**Brief Pain Inventory -** This scale asks you about your pain and asks you to indicate where you are experiencing pain on a body map image.

**Body Perception -** This scale asks you how aware you are of different bodily sensations and processes.

**Depression Anxiety Stress Scale -** This scale asks you to indicate how you have been feeling over the last week.

**Multidimensional Assessment of Interoceptive Awareness -** This scale asks you to indicate how often you feel certain ways in your general daily life.

**Sensitisation Inventory -** This scale asks you how much you have felt a particular way in the last month.

**Pain Distress Scale -** This scale asks you about the types of thoughts and feelings that you have when you are in pain.

**Positive and Negative Affect Schedule -** This scale asks you to what extent you are currently experiencing specific feelings and emotions.

**Pittsburgh Sleep Quality Index -** This index asks you about your usual sleep habits during the past month.

What is the highest level of education you have attained?

- ○ Some high school
- ○ High school or equivalent
- ○ Trade/technical/vocational training (e.g. TAFE course)
- ○ Some university study
- ○ Bachelor's degree
- ○ Master's degree
- ○ Doctorate degree
- ○ [ ] Other (please specify)

What is your current employment?

What is your Postcode?

Is English your first language?

- ○ Yes
- ○ No

**Demographics**

How would you say you are managing financially at the moment?

- ○ Living comfortably
- ○ Getting by
- ○ Finding it difficult

Do you have access to an Australian Healthcare Card? (the Healthcare card assists Government benefit recipients, low income earners and selected other groups with access to cheaper Government-subsidised prescription medicines and a lower Extended Medicare Safety Net threshold)

- ○ Yes

- ○ No

Medical diagnoses (Check all that apply)

- ☐ Neurological conditions such as schizophrenia, epilepsy, stroke, etc. Please specify
- ☐ Psychiatric conditions such as post-traumatic stress disorder, anxiety disorder, panic disorder, depression, obsessive-compulsive disorder. Please specify
- ☐ Musculoskeletal disorders such as arthritis, other muscle or joint pain, etc. Please specify
- ☐ Other conditions not listed above. Please specify

Hormonal status (please check one)

- ○ Still having menstrual cycles; if so, days since last menses started
- ○ Currently pregnant or breast feeding
- ○ Currently peri-menopausal (irregular menses due to peri-menopause)
- ○ Post-menopausal, naturally (no menses for at least 12 months)
- ○ Post-menopausal due to surgery
- ○ Other

Are you on any hormonal treatment containing estradiol either for treatment of a condition, hormone replacement, or contraception?

- ○ Yes
- ○ No

Do you smoke or use nicotine-containing products?

- ○ Yes (Amount)
- ○ No

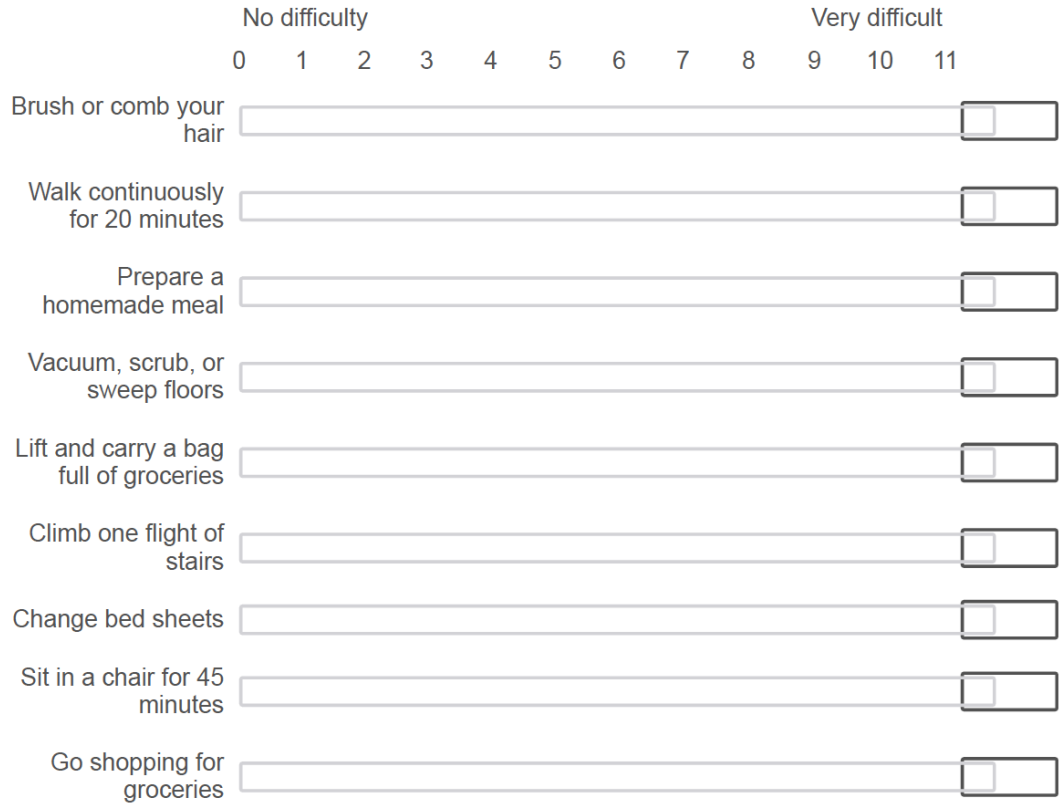
Do you use any recreational drugs?

- ○ Yes

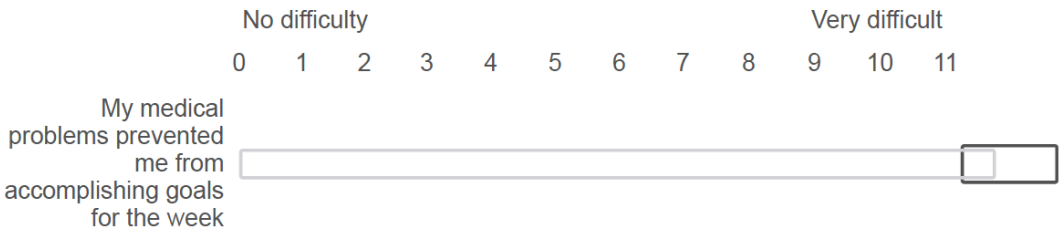
○ No

**SIQ-R**

For each of the following nine statements, drag the slider to where you feel best indicates how much difficulty you have experienced in doing the following activities during the past 7 days. If you did not perform a particular activity in the last 7 days, rate the difficulty for the last time you performed the activity. If you can't perform an activity, check the last box.




For the following two statements, drag the slider to where you feel best describes the overall impact of any medical problems over the last seven days:






For the following ten statements, drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:




Please drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:



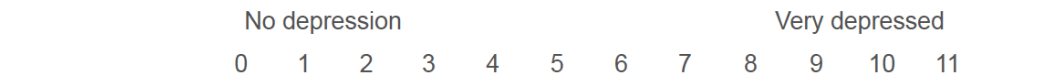

Please drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:




Please drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:




Please drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:






Please drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:




Please drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:




Please drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:




Please drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:




Please drag the slider to where you feel best indicates the intensity of the following common symptoms over the last seven days:

No sensitivity Extreme sensitivity



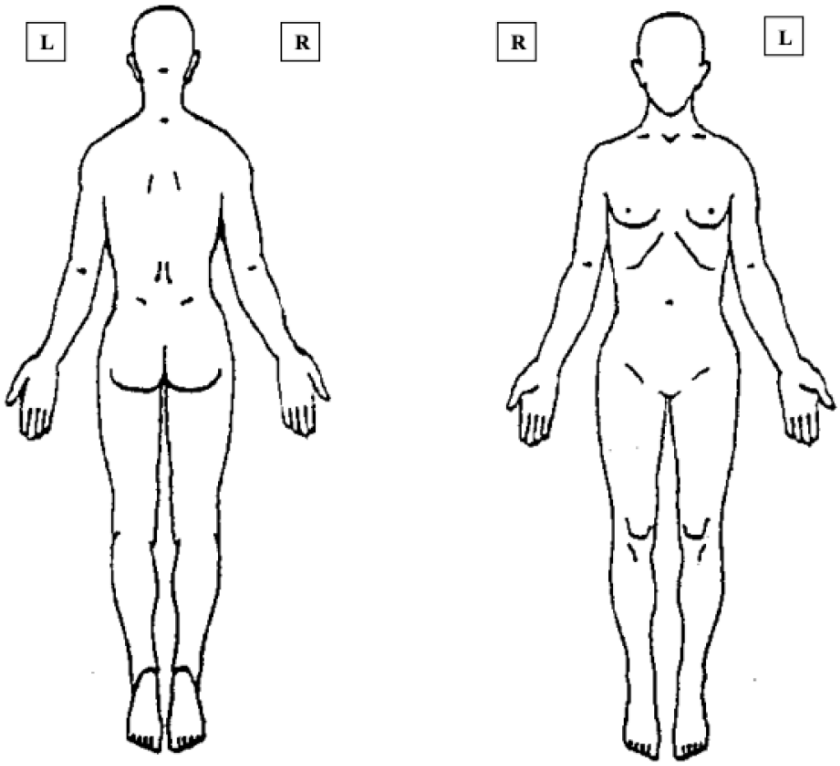

Please rate your level of sensitivity to loud noises, bright lights, odours, and cold

**Brief pain inventory**

Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

- ○ Yes
- ○ No

On the diagram, click on the areas where you feel pain. Please note, we are only able to allow 10 markings - if you require more, you can generalise the area or clarify in the text box below.




Please leave any additional information here as well as indicating which are you experience the most pain.

Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the las 24 hours.

No pain Pain as bad as you can imagine

0 1 2 3 4 5 6 7 8 9 10

Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the las 24 hours.

No pain — Pain as bad as you can imagine

0 1 2 3 4 5 6 7 8 9 10

Please rate your pain by marking the box beside the number that best describes your pain **on average.**

No pain — Pain as bad as you can imagine

0 1 2 3 4 5 6 7 8 9 10

Please rate your pain by marking the box beside the number that tells how much pain you have **right now.**

No pain — Pain as bad as you can imagine

0 1 2 3 4 5 6 7 8 9 10

What treatments or medications are you receiving for your pain?

In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the number that most shows how much **relief** you have received.

No relief — Complete relief

0 1 2 3 4 5 6 7 8 9 10

Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

| | Does not interfere 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Completely interferes 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| General activity | | | | | | | | | | | ☐ |
| Mood | | | | | | | | | | | ☐ |
| Walking ability | | | | | | | | | | | ☐ |
| Normal work (both inside and outside of the home) | | | | | | | | | | | ☐ |
| Relationships with other people | | | | | | | | | | | ☐ |
| Sleep | | | | | | | | | | | ☐ |
| Enjoyment of life | | | | | | | | | | | ☐ |

## Body Perception

Imagine how aware you are of your body processes. Select the answer that most accurately describes you. Rate your awareness on each of the characteristics described below by ticking in the column that best describes your awareness.

During most situations I am aware of:

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Swallowing frequently | ○ | ○ | ○ | ○ | ○ |
| A ringing in my ears | ○ | ○ | ○ | ○ | ○ |
| An urge to cough to clear my throat | ○ | ○ | ○ | ○ | ○ |
| My body swaying when I am standing | ○ | ○ | ○ | ○ | ○ |
| My mouth being dry | ○ | ○ | ○ | ○ | ○ |
| How fast I am breathing | ○ | ○ | ○ | ○ | ○ |
| Watering or tearing of my eyes | ○ | ○ | ○ | ○ | ○ |
| My skin itching | ○ | ○ | ○ | ○ | ○ |
| | Never | Occasionally | Sometimes | Usually | Always |
| Noises associated with my digestion | ○ | ○ | ○ | ○ | ○ |
| Eye fatigue or pain | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Muscle tension in my back and neck | ○ | ○ | ○ | ○ | ○ |
| A swelling of my body or parts of my body | ○ | ○ | ○ | ○ | ○ |
| An urge to urinate | ○ | ○ | ○ | ○ | ○ |
| Tremor in my hands | ○ | ○ | ○ | ○ | ○ |
| An urge to defaecate | ○ | ○ | ○ | ○ | ○ |
| Muscle tension in my arms and legs | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| A bloated feeling because of water retention | ○ | ○ | ○ | ○ | ○ |
| Muscle tension in my face | ○ | ○ | ○ | ○ | ○ |
| Goose bumps | ○ | ○ | ○ | ○ | ○ |
| Facial twitches | ○ | ○ | ○ | ○ | ○ |
| Being exhausted | ○ | ○ | ○ | ○ | ○ |
| Stomach and gut pains | ○ | ○ | ○ | ○ | ○ |
| Rolling or fluttering in my eyes | ○ | ○ | ○ | ○ | ○ |
| Stomach distension or bloatedness | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Palms sweating | ○ | ○ | ○ | ○ | ○ |
| Sweat on my forehead | ○ | ○ | ○ | ○ | ○ |
| Clumsiness or bumping into people | ○ | ○ | ○ | ○ | ○ |
| Tremor in my lips | ○ | ○ | ○ | ○ | ○ |
| Sweat in my armpits | ○ | ○ | ○ | ○ | ○ |
| Sensations of prickling, tingling, or numbness in my body | ○ | ○ | ○ | ○ | ○ |
| The temperature of my face (especially my ears) | ○ | ○ | ○ | ○ | ○ |
| Grinding my teeth | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| General jitteriness | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Muscle pain | ○ | ○ | ○ | ○ | ○ |
| Joint pain | ○ | ○ | ○ | ○ | ○ |
| Fullness of bladder | ○ | ○ | ○ | ○ | ○ |
| My eye movements | ○ | ○ | ○ | ○ | ○ |
| Back pain | ○ | ○ | ○ | ○ | ○ |
| My nose itching | ○ | ○ | ○ | ○ | ○ |
| The hair on the back of my neck "standing up" | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Needing to rest | ○ | ○ | ○ | ○ | ○ |
| Difficulty in focusing | ○ | ○ | ○ | ○ | ○ |
| An urge to swallow | ○ | ○ | ○ | ○ | ○ |
| How hard my heart is beating | ○ | ○ | ○ | ○ | ○ |
| Feeling constipated | ○ | ○ | ○ | ○ | ○ |

Imagine yourself in a very stressful situation or during period of severe stress. Using the following 5 point scale, rate your awareness of perceived changes due to stress in each of the global response systems described below.

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Vascular responses such as my face becoming flushed or pallid, or feeling faint | ○ | ○ | ○ | ○ | ○ |
| Body posture shifts such as being hunched over, head down and knees locked | ○ | ○ | ○ | ○ | ○ |
| Muscle tone or tremor such as arms and legs feeling weak, hands shaking and lips quivering | ○ | ○ | ○ | ○ | ○ |
| Breathing more rapidly and shallowly, and having difficulty in catching my breath | ○ | ○ | ○ | ○ | ○ |
| Digestive responses including gastric distress, gas cramps and diarrhea | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| | Never | Occasionally | Sometimes | Usually | Always |
| Difficulty in paying attention with my mind wandering or daydreaming | ○ | ○ | ○ | ○ | ○ |
| Difficulties in sensory abilities such as problems hearing, seeing, smelling or feeling touch | ○ | ○ | ○ | ○ | ○ |
| Emotional problems such as more frequent feelings of depression, frustration, rage or anger | ○ | ○ | ○ | ○ | ○ |
| Difficulty organising my thoughts | ○ | ○ | ○ | ○ | ○ |
| Difficulty speaking clearly and understandably | ○ | ○ | ○ | ○ | ○ |

The autonomic nervous system is the part of your nervous system that controls your cardiovascular, respiratory, digestive and temperature regulation systems. It is also involved in the experience and expression of emotions. The autonomic nervous system functions differently amongst people. This scale has been developed to measure how your autonomic nervous system reacts.

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| I feel nauseous | ○ | ○ | ○ | ○ | ○ |
| I have difficulty coordinating breathing and eating | ○ | ○ | ○ | ○ | ○ |
| My nose is runny even when I am not sick | ○ | ○ | ○ | ○ | ○ |
| When I am eating I have difficulty talking | ○ | ○ | ○ | ○ | ○ |
| My heart beats irregularly | ○ | ○ | ○ | ○ | ○ |
| When I eat, food feels dry and sticks to my mouth and throat | ○ | ○ | ○ | ○ | ○ |
| I have "sour" stomach | ○ | ○ | ○ | ○ | ○ |
| | Never | Occasionally | Sometimes | Usually | Always |
| I feel like vomiting | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| I feel shortness of breath | ○ | ○ | ○ | ○ | ○ |
| I have difficulty coordinating breathing with talking | ○ | ○ | ○ | ○ | ○ |
| When I eat, I have difficulty coordinating swallowing, chewing and/or sucking with breathing | ○ | ○ | ○ | ○ | ○ |
| I have a persistent cough that interferes with my talking and eating | ○ | ○ | ○ | ○ | ○ |
| I drool especially when I am excited | ○ | ○ | ○ | ○ | ○ |
| I gag from the saliva in my mouth | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| I produce a lot of saliva even when I am not eating | ○ | ○ | ○ | ○ | ○ |
| I have difficulty adjusting my eyes to changes in illumination | ○ | ○ | ○ | ○ | ○ |
| I have chest pains | ○ | ○ | ○ | ○ | ○ |
| I gag when I eat | ○ | ○ | ○ | ○ | ○ |
| When I talk, I often feel I should cough or swallow the saliva in my mouth | ○ | ○ | ○ | ○ | ○ |
| I am constipated | ○ | ○ | ○ | ○ | ○ |
| I have indigestion | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| After eating I have digestive problems | ○ | ○ | ○ | ○ | ○ |
| I have diarrhoea | ○ | ○ | ○ | ○ | ○ |
| When I breathe, I feel like I cannot get enough oxygen | ○ | ○ | ○ | ○ | ○ |
| I have difficulty controlling my eyes | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| I get dizzy when urinating or having a bowel movement | ○ | ○ | ○ | ○ | ○ |
| I have trouble focusing when I go into dimly or brightly illuminated places | ○ | ○ | ○ | ○ | ○ |

Each of us responds differently to stressful events and conditions. The Stress Styles I scale evaluates your style of responding to stress.
Using the 5 point scale rate yourself on the questions below

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| I approach the problem head on | ○ | ○ | ○ | ○ | ○ |
| I withdraw | ○ | ○ | ○ | ○ | ○ |
| I know that things will get better later, so I wait until I feel better before acting | ○ | ○ | ○ | ○ | ○ |
| I know that things will go better if I act immediately | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| I feel mental tension | ○ | ○ | ○ | ○ | ○ |
| I feel frustrated | ○ | ○ | ○ | ○ | ○ |
| I feel insecure | ○ | ○ | ○ | ○ | ○ |
| I feel aimless | ○ | ○ | ○ | ○ | ○ |

Each of us responds differently to stressful events and conditions. The Stress Styles I Scale evaluates your style of responding to stress.
Using the 5 point scale, rate yourself on each of the statements below

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| I feel dizzy | ○ | ○ | ○ | ○ | ○ |
| I have difficulty speaking | ○ | ○ | ○ | ○ | ○ |
| I feel a tingling in my face | ○ | ○ | ○ | ○ | ○ |
| I feel my blood sugar drop | ○ | ○ | ○ | ○ | ○ |

I experience, have experienced or have been diagnosed as having:

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Migraine headaches | ○ | ○ | ○ | ○ | ○ |
| Gastric distress or digestive problems | ○ | ○ | ○ | ○ | ○ |
| Arthritis | ○ | ○ | ○ | ○ | ○ |
| Hypertension | ○ | ○ | ○ | ○ | ○ |
| Hopeless unhappiness | ○ | ○ | ○ | ○ | ○ |
| Clinical depression | ○ | ○ | ○ | ○ | ○ |
| Bulimia | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Anorexia | ○ | ○ | ○ | ○ | ○ |
| Obesity | ○ | ○ | ○ | ○ | ○ |
| Asthma | ○ | ○ | ○ | ○ | ○ |
| Endocrine problems (e.g. thyroid, adrenal or gonadal hormone dysfunction) | ○ | ○ | ○ | ○ | ○ |
| Eczema | ○ | ○ | ○ | ○ | ○ |
| Oedema | ○ | ○ | ○ | ○ | ○ |
| Back problems | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Diabetes | ○ | ○ | ○ | ○ | ○ |
| Epilepsy | ○ | ○ | ○ | ○ | ○ |
| Cancer | ○ | ○ | ○ | ○ | ○ |
| Hypoglycemia | ○ | ○ | ○ | ○ | ○ |
| Heart disease | ○ | ○ | ○ | ○ | ○ |
| Stroke | ○ | ○ | ○ | ○ | ○ |
| Gastric and duodenal ulcers | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Psychiatric disorders | ○ | ○ | ○ | ○ | ○ |
| Pneumonia | ○ | ○ | ○ | ○ | ○ |
| Heart attack | ○ | ○ | ○ | ○ | ○ |
| Motion sickness | ○ | ○ | ○ | ○ | ○ |
| Premenstrual syndrome | ○ | ○ | ○ | ○ | ○ |
| Sever menstrual cramps | ○ | ○ | ○ | ○ | ○ |

| | Never | Occasionally | Sometimes | Usually | Always |
|---|---|---|---|---|---|
| Post-partum depression | ○ | ○ | ○ | ○ | ○ |

**DASS-21**

Please read each statement and select the answer that most accurately describes you by ticking in the column which indicates how much statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement. The rating scale is as follows:

Did not apply to me at all - NEVER
Applied to me to some degree, or some of the time - SOMETIMES
Applied to me to a considerable degree, or a good part of time - OFTEN
Applied to me very much, or most of the time - ALMOST ALWAYS

| | Never | Sometimes | Often | Almost always |
|---|---|---|---|---|
| I found it hard to wind down | ○ | ○ | ○ | ○ |
| I was aware of dryness of my mouth | ○ | ○ | ○ | ○ |
| I couldn't seem to experience any positive feeling at all | ○ | ○ | ○ | ○ |
| I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion) | ○ | ○ | ○ | ○ |
| I found it difficult to do things | ○ | ○ | ○ | ○ |
| I tended to over-react to situations | ○ | ○ | ○ | ○ |
| I experienced trembling (e.g. in the hands) | ○ | ○ | ○ | ○ |
| I felt that I was using a lot of nervous energy | ○ | ○ | ○ | ○ |

| | Never | Sometimes | Often | Almost always |
|---|---|---|---|---|
| I was worried about situations in which I might panic and make a fool of myself | ○ | ○ | ○ | ○ |
| I felt that I had nothing to look forward to | ○ | ○ | ○ | ○ |
| I found myself getting agitated | ○ | ○ | ○ | ○ |
| I found it difficult to relax | ○ | ○ | ○ | ○ |
| I felt down-hearted and blue | ○ | ○ | ○ | ○ |
| I was intolerant of anything that kept me from getting on with what I was doing | ○ | ○ | ○ | ○ |
| I felt I was close to panic | ○ | ○ | ○ | ○ |
| I was unable to become enthusiastic about anything | ○ | ○ | ○ | ○ |
| I felt I wasn't worth much as a person | ○ | ○ | ○ | ○ |
| I felt that I was rather touchy | ○ | ○ | ○ | ○ |
| I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat) | ○ | ○ | ○ | ○ |
| I felt scared without any good reason | ○ | ○ | ○ | ○ |
| I felt that life was meaningless | ○ | ○ | ○ | ○ |

## MAIA-2

Below you will find a list of statements. Please indicate how often each statement applies to you generally in daily life.

| 0 (Never) | 1 | 2 | 3 | 4 | 5 (Always) |
|---|---|---|---|---|---|

| | 0 (Never) | 1 | 2 | 3 | 4 | 5 (Always) |
|---|---|---|---|---|---|---|
| When I am tense I notice where the tension is located in my body. | ○ | ○ | ○ | ○ | ○ | ○ |
| I notice when I am uncomfortable in my body. | ○ | ○ | ○ | ○ | ○ | ○ |
| I noticed where in my body I am comfortable. | ○ | ○ | ○ | ○ | ○ | ○ |
| I notice changes in my breathing, such as whether it slows down or speeds up. | ○ | ○ | ○ | ○ | ○ | ○ |
| I ignore physical tension or discomfort until they become more severe. | ○ | ○ | ○ | ○ | ○ | ○ |
| I distract myself from sensations of discomfort. | ○ | ○ | ○ | ○ | ○ | ○ |
| When I feel pain or discomfort, I try to power through it. | ○ | ○ | ○ | ○ | ○ | ○ |
| I try to ignore pain. | ○ | ○ | ○ | ○ | ○ | ○ |
| | 0 (Never) | 1 | 2 | 3 | 4 | 5 (Always) |
| I push feelings of discomfort away by focusing on something. | ○ | ○ | ○ | ○ | ○ | ○ |
| When I feel unpleasant body sensations, I occupy myself with something else so I don't have to feel them. | ○ | ○ | ○ | ○ | ○ | ○ |
| When I feel physical pain, I become upset. | ○ | ○ | ○ | ○ | ○ | ○ |
| I start to worry that something is wrong if I feel any discomfort. | ○ | ○ | ○ | ○ | ○ | ○ |
| I can notice an unpleasant body sensation without worrying about it. | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (Never) | 1 | 2 | 3 | 4 | 5 (Always) |
|---|---|---|---|---|---|---|
| I can stay calm and not worry when I have feelings of discomfort or pain. | ○ | ○ | ○ | ○ | ○ | ○ |
| When I am in discomfort or pain I can't get it out of my mind. | ○ | ○ | ○ | ○ | ○ | ○ |
| I can pay attention to my breath without being distracted by things happening around me. | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (Never) | 1 | 2 | 3 | 4 | 5 (Always) |
|---|---|---|---|---|---|---|
| I can maintain awareness of my inner bodily sensations even when there is a lot going on around me. | ○ | ○ | ○ | ○ | ○ | ○ |
| When I am in conversation with someone, I can pay attention to my posture. | ○ | ○ | ○ | ○ | ○ | ○ |
| I can return awareness to my body if I am distracted. | ○ | ○ | ○ | ○ | ○ | ○ |
| I can refocus my attention from thinking to sensing my body. | ○ | ○ | ○ | ○ | ○ | ○ |
| I can maintain awareness of my whole body even when a part of me is in pain or discomfort. | ○ | ○ | ○ | ○ | ○ | ○ |
| I am able to consciously focus on my body as a whole. | ○ | ○ | ○ | ○ | ○ | ○ |
| I notice how my body changes when I am angry. | ○ | ○ | ○ | ○ | ○ | ○ |
| When something is wrong in my life I can feel it in my body. | ○ | ○ | ○ | ○ | ○ | ○ |

| | 0 (Never) | 1 | 2 | 3 | 4 | 5 (Always) |
|---|---|---|---|---|---|---|

| | 0 (Never) | 1 | 2 | 3 | 4 | 5 (Always) |
|---|---|---|---|---|---|---|
| I notice that my body feels different after a peaceful experience. | ○ | ○ | ○ | ○ | ○ | ○ |
| I notice that my breathing becomes free and easy when I feel comfortable. | ○ | ○ | ○ | ○ | ○ | ○ |
| I notice how my body changes when I feel happy/joyful. | ○ | ○ | ○ | ○ | ○ | ○ |
| When I feel overwhelmed I can find a calm place inside. | ○ | ○ | ○ | ○ | ○ | ○ |
| When I bring awareness to my body I feel a sense of calm. | ○ | ○ | ○ | ○ | ○ | ○ |
| I can use my breath to reduce tension. | ○ | ○ | ○ | ○ | ○ | ○ |
| When I am caught up in my thoughts, I can calm my mind by focusing on my body/breathing. | ○ | ○ | ○ | ○ | ○ | ○ |
| I listen for information from my body about my emotional state. | ○ | ○ | ○ | ○ | ○ | ○ |
| | 0 (Never) | 1 | 2 | 3 | 4 | 5 (Always) |
| When I am upset, I take time to explore how my body feels. | ○ | ○ | ○ | ○ | ○ | ○ |
| I listen to my body to inform me about what to do. | ○ | ○ | ○ | ○ | ○ | ○ |
| I am at home in my body. | ○ | ○ | ○ | ○ | ○ | ○ |
| I feel my body is a safe place. | ○ | ○ | ○ | ○ | ○ | ○ |
| I trust my body sensations. | ○ | ○ | ○ | ○ | ○ | ○ |

**Sensitization Inventory**

Please circle the best response to the right of each statement for how you have felt in the past month (except for the second to last item which is personal history)

| | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|
| I feel tired and unrefreshed when I wake from sleeping | ○ | ○ | ○ | ○ | ○ |
| My muscles feel stiff and achy | ○ | ○ | ○ | ○ | ○ |
| I have anxiety attacks | ○ | ○ | ○ | ○ | ○ |
| I grind or clench my teeth | ○ | ○ | ○ | ○ | ○ |
| I have problems with diarrhoea and constipation | ○ | ○ | ○ | ○ | ○ |
| I need help in performing my daily activities | ○ | ○ | ○ | ○ | ○ |
| I am sensitive to bright lights | ○ | ○ | ○ | ○ | ○ |
| I get tired very easily when I am physically active | ○ | ○ | ○ | ○ | ○ |
| I feel pain all over my body | ○ | ○ | ○ | ○ | ○ |
| I have headaches | ○ | ○ | ○ | ○ | ○ |
| I feel discomfort in my bladder and/or burning when I urinate | ○ | ○ | ○ | ○ | ○ |
| I do not sleep well | ○ | ○ | ○ | ○ | ○ |
| I have difficulty concentrating | ○ | ○ | ○ | ○ | ○ |
| I have skin problems such as dryness, itchiness, or rashes | ○ | ○ | ○ | ○ | ○ |
| Stress makes my physical symptoms get worse | ○ | ○ | ○ | ○ | ○ |
| I feel sad or depressed | ○ | ○ | ○ | ○ | ○ |
| I have low energy | ○ | ○ | ○ | ○ | ○ |
| I have muscle tension in my neck and shoulders | ○ | ○ | ○ | ○ | ○ |
| I have pain in my jaw | ○ | ○ | ○ | ○ | ○ |
| Certain smells, such as perfumes, make me feel dizzy and nauseated | ○ | ○ | ○ | ○ | ○ |

| | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|
| I have to urinate frequently | ○ | ○ | ○ | ○ | ○ |
| My legs feel uncomfortable and restless when I am trying to go to sleep at night | ○ | ○ | ○ | ○ | ○ |
| I have difficulty remembering things | ○ | ○ | ○ | ○ | ○ |
| I suffered trauma as a child | ○ | ○ | ○ | ○ | ○ |
| I have pain in my pelvic area | ○ | ○ | ○ | ○ | ○ |

## Pain Distress Scale

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

Instructions: We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain.

Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

| | Not at all | To a slight degree | To a moderate degree | To a great degree | All the time |
|---|---|---|---|---|---|
| I worry all the time about whether the pain will end | ○ | ○ | ○ | ○ | ○ |
| I feel I can't go on | ○ | ○ | ○ | ○ | ○ |
| It's terrible and I think it's never going to get any better | ○ | ○ | ○ | ○ | ○ |
| It's awful and I feel that it overwhelms me | ○ | ○ | ○ | ○ | ○ |
| I feel I can't stand it anymore | ○ | ○ | ○ | ○ | ○ |
| I become afraid that the pain will get worse | ○ | ○ | ○ | ○ | ○ |

| | Not at all | To a slight degree | To a moderate degree | To a great degree | All the time |
|---|---|---|---|---|---|
| I keep thinking of other painful events | ○ | ○ | ○ | ○ | ○ |
| I anxiously want the pain to go away | ○ | ○ | ○ | ○ | ○ |
| I can't seem to keep it out of my mind | ○ | ○ | ○ | ○ | ○ |
| I keep thinking about how much it hurts | ○ | ○ | ○ | ○ | ○ |
| I keep thinking about how badly I want the pain to stop | ○ | ○ | ○ | ○ | ○ |
| There's nothing I can do to reduce the intensity of the pain | ○ | ○ | ○ | ○ | ○ |
| I wonder whether something serious may happen | ○ | ○ | ○ | ○ | ○ |

## PANAS

This scale consists of a number of words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. Indicate to what extent you feel this way right now, that is, at the present moment.

| | Very slightly or not at all | A little | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|
| Interested | ○ | ○ | ○ | ○ | ○ |
| Distressed | ○ | ○ | ○ | ○ | ○ |
| Excited | ○ | ○ | ○ | ○ | ○ |
| Upset | ○ | ○ | ○ | ○ | ○ |
| Strong | ○ | ○ | ○ | ○ | ○ |
| Guilty | ○ | ○ | ○ | ○ | ○ |
| Scared | ○ | ○ | ○ | ○ | ○ |
| Hostile | ○ | ○ | ○ | ○ | ○ |
| Enthusiastic | ○ | ○ | ○ | ○ | ○ |
| Proud | ○ | ○ | ○ | ○ | ○ |
| Irritable | ○ | ○ | ○ | ○ | ○ |
| Alert | ○ | ○ | ○ | ○ | ○ |
| Ashamed | ○ | ○ | ○ | ○ | ○ |
| Inspired | ○ | ○ | ○ | ○ | ○ |

| | Very slightly or not at all | A little | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|
| Nervous | ○ | ○ | ○ | ○ | ○ |
| Determined | ○ | ○ | ○ | ○ | ○ |
| Attentive | ○ | ○ | ○ | ○ | ○ |
| Jittery | ○ | ○ | ○ | ○ | ○ |
| Active | ○ | ○ | ○ | ○ | ○ |
| Afraid | ○ | ○ | ○ | ○ | ○ |

**Distress Screen**

In your life, have you ever had any experience that was so frightening, horrible, or upsetting that, in the past month, you (select the most appropriate response):

| | YES | NO |
|---|---|---|
| Have had nightmares about it or thought about it when you did not want to? | ○ | ○ |
| Tried hard not to think about it or went out of your way to avoid situations that reminded you of it? | ○ | ○ |
| Were constantly on guard, watchful, or easily startled? | ○ | ○ |
| Felt numb or detached from others, activities, or your surroundings? | ○ | ○ |

**PSQI**

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month, when have you gone to bed?

How long in minutes has it taken you to fall asleep each night?

When have you usually gotten up in the morning?

How many hours of actual sleep did you get that night? (This may be different to the number of hours you spend in bed)

During the past month, how often have you had trouble sleeping because you...

| | Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
|---|---|---|---|---|
| Cannot get to sleep within 30 minutes | ○ | ○ | ○ | ○ |
| Wake up in the middle of the night or early morning | ○ | ○ | ○ | ○ |
| Have to get up to use the bathroom | ○ | ○ | ○ | ○ |
| Cannot breathe comfortably | ○ | ○ | ○ | ○ |
| Cough or snore loudly | ○ | ○ | ○ | ○ |
| Feel too cold | ○ | ○ | ○ | ○ |
| Feel too hot | ○ | ○ | ○ | ○ |
| Have bad dreams | ○ | ○ | ○ | ○ |
| Have pain | ○ | ○ | ○ | ○ |
| Other reason(s), please describe | ○ | ○ | ○ | ○ |

During the past month, how often have you...

| | Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
|---|---|---|---|---|
| Taken medicine (prescribed or "over the counter") to help you sleep? | ○ | ○ | ○ | ○ |

During the past month, how often have you had trouble staying awake while...

| | Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
|---|---|---|---|---|
| Driving, eating meals, or engaging in social activities? | ○ | ○ | ○ | ○ |

During the past month, how much of a problem has it been...

| | A great deal | A lot | A moderate amount | A little | None at all |
|---|---|---|---|---|---|
| For you to keep up enthusiasm to get things done? | ○ | ○ | ○ | ○ | ○ |

During the past month, how would you rate your sleep quality overall?

- ○ Very good
- ○ Fairly good
- ○ Fairly bad
- ○ Very bad

**WNS-6B Noise Sensitivity Scale**

Select the response that most accurately reflects how you felt this week:

| | YES | NO |
|---|---|---|
| I am easily awakened by noise | ○ | ○ |
| I get used to most noises without much difficulty | ○ | ○ |
| I find it hard to relax in a place that's noisy | ○ | ○ |
| I'm good at concentrating no matter what is going on around me | ○ | ○ |
| I get mad at people who make noise that keeps me from falling asleep or getting work done | ○ | ○ |
| I am sensitive to noise | ○ | ○ |

**Distress Protocol**

**Are you concerned about your mental health?**

As part of this study, we are using questionnaires to assess different aspects of your life. These measures should not be considered a clinical assessment; rather it is only being used for research purposes.

We recognise that some people who take part in this study may have concerns about their health and wellbeing. If you have any concerns regarding your mental health we would strongly encourage you to seek help.

**Where to start?**
If you have a good relationship with your GP, you should discuss your problems with them, if you have not already done so. Your GP can also arrange a referral to an appropriate specialist if this is considered useful. Visits to a psychologist or psychiatrist can be arranged through a mental health care plan, giving you access to 20 appointments per calendar year, at a subsidised cost to you.

Alternatively, you can call the mental health triage service on **13 14 65 (available 24 hours, seven days a week)**. The nurse on triage will discuss your particular problems with you and arrange for a referral to the appropriate team.

**Important!**
If you are uncertain about the seriousness of your problems or if you are in any doubt at all about whether you should ring – then the best thing to do is to ring 13 14 65 and talk to one of the nurses. Our experience has been that they are very supportive and helpful.

Other contacts that you may find helpful are:

- **ACIS** (Acute Crisis Intervention Service: Adult Mental Heath): 13 14 65
- **Lifeline**: 13 11 14
- **Emergency and Crisis Intervention**: 13 14 65
- **Crisis Care** (4pm-9am): 13 16 11
- **Older Persons Mental Health Service** (OPMHS): (08) 8426 0600; developed specifically for people aged 65 years + to assist in mental health assessments, treatment and care planning.

If you have access to the internet, the Australian Psychological Society provides information about Psychologists available in your area:
**https://www.psychology.org.au/FindaPsychologist/**

For information about Australia wide services refer to: Searching for help:
**http://www.searchingforhelp.com.au/**

## End of Survey

You have completed the survey. Thank you for your time and effort. If you have any queries, you may ask them in the box below or speak to the researcher via phone or email.

To end this survey, you can now close this window.

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# Appendix 11 – Research Dissemination

11.1 Co-author publications produced during candidature, but not included in this thesis

11.2 Oral abstract presentations (peer reviewed)

11.3 Poster abstract presentations (peer reviewed)

11.4 Poster Presentation – the Australian Society for Social and Affective Neuroscience 2022, Sydney, Australia.

11.5 Poster Presentation – Australian Pain Society Annual Scientific Meeting 2022, Tasmania, Australia.

11.6 Rapid Talk APS 2022 – Study 2: Most frequently reported areas of pain in people living with fibromyalgia represented on drawing of a woman (Poster # 76)

11.7 Additional activities during candidature

- 11.7.1 Certificates and workshops
- 11.7.2 Community outreach and engagement

### 11.1. Co-author publications produced during candidature, but not included in this thesis

Bornkessel-Schlesewsky, I., Alday, P. M., Corcoran, A. W., Wilkinson, E. M., Sharrad, I., Kliegl, R., Lewis, R. L., Small, S. L., Schlesewsky, M. (2022). Effects of neural noise on predictive model updating across the adult lifespan. bioRxiv [Under Review], Doi: 10.1101/2022.12.14.520501

Bornkessel-Schlesewsky, I., Sharrad, I., Howlett, C., Alday, P. M., Corcoran, A. W., Bellan, V., Wilkinson, E. M., Kliegl, R., Lewis, R. K., Small, S. L., Schlesewsky, M. (2022). Rapid adaptation of predictive models during language comprehension: Aperiodic EEG slope, individual alpha frequency and idea density modulate individual differences in real-time model updating. *Frontiers in Psychology*. Doi: 10.3389/fpsyg.2022.817516

Bellan, V., Braithwaite, F. A., Wilkinson, E. M., Stanton, T. R., Moseley, G. L. (2021). Where is my arm? Investigating the link between complex regional pain syndrome and poor localisation of the affected limb. *PeerJ*. Doi: 10.7717/peerj.11882

Cross, Z. R., Zou-Williams, L., Wilkinson, E., Schlesewsky, M., & Bornkessel-Schlesewsky, I. (2020). Mini Pinyin: A modified miniature language for studying language learning and incremental sentence processing. *Behaviour Research Methods*. Doi: 10.3758/s13428-020-01473-6

### 11.2 Oral abstract presentations (peer reviewed)

Wilkinson, E. M. (2022, April). *Sensing the Body in Pain: Body Perception and Pain across Conditions*. **Rapid Talk** presented at the Australian Pain Society Annual Scientific Meeting 2022, Tasmania, Australia.

Wilkinson, E. M. (2021, June). *An Investigation of Brain-Body Integration in Fibromyalgia using Upper Limb Tasks*. **Video Presentation** presented at the International Association for the Study of Pain 2021 Virtual World Congress on Pain, online.

Wilkinson, E. M. (2020, April). *Visuo-proprioceptive incongruence and self-localisation in CRPS*. **Rapid Talk** at the Australian Pain Society, Tasmania, Australia. [Cancelled due to COVID-19 Restrictions]

### 11.3 Poster abstract presentations (peer reviewed)

Wilkinson, E. M. (2022, May). *Interoception in Health and Disease: A meta-analytical review of the neurophysiological properties of the heartbeat evoked potential*. **Poster session** presented at the Australian Society for Social and Affective Neuroscience 2022, Sydney, Australia.

Wilkinson, E. M. (2022, April). *Sensing the Body in Pain: Body Perception and Pain across Conditions*. **Poster session** presented at the Australian Pain Society Annual Scientific Meeting 2022, Tasmania, Australia.

Wilkinson, E. M. (2021, June). *An Investigation of Brain-Body Integration in Fibromyalgia using Upper Limb Tasks*. **Poster session** presented at the International Association for the Study of Pain 2021 Virtual World Congress on Pain, online.

Wilkinson, E. M. (2020, April). *Visuo-proprioceptive incongruence and self-localisation in CRPS.* **Poster session** at the Australian Pain Society, Tasmania, Australia. [Cancelled due to COVID-19 Restrictions]

## 11.4 Poster Presentation – the Australian Society for Social and Affective Neuroscience 2022, Sydney, Australia.

# INTEROCEPTION IN HEALTH AND DISEASE:

## A meta-analytical review of the neurophysiological properties of the heartbeat evoked potential

Erica M. Wilkinson[a], Mark Kohler[b], G. Lorimer Moseley[a], Carolyn Berryman[a]

[a] IIMPACT in Health, University of South Australia, Kaurna Country, Adelaide, Australia

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**Interoception varies as a function of clinical and testing condition**

**Methodological inconsistencies may contribute to the variability of results, and by extension, limit the potential clinical inferences that can be drawn.**

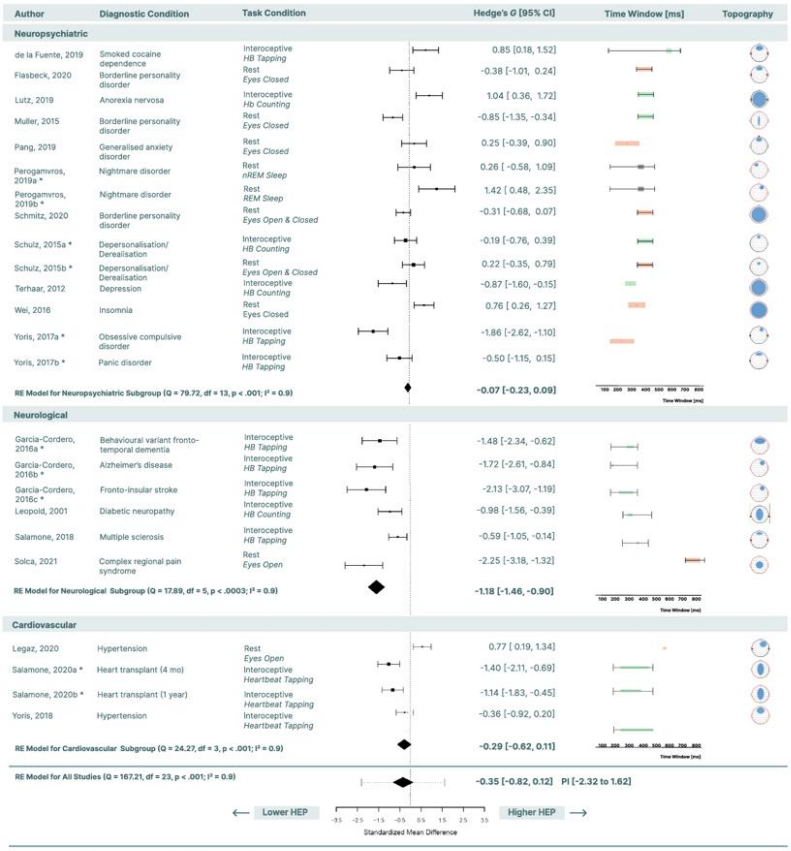



**Table 1. Forest Plot of Subgroup Analysis: Diagnostic Condition**

The estimates left of 0 indicate lower HEP amplitude in the clinical group compared to their healthy comparison group. The estimates right of 0 indicate higher HEP amplitude in the clinical group compared to their healthy comparison group. Additional variables (task condition, time window, and topography) have been included to demonstrate the variability in methodological decisions. The time window panel illustrates both the time window investigated (black line) and the time window that HEP was reported (coloured line). Line colour indicates the task condition (green for interoceptive task and red for resting state task). Prediction intervals denoted by horizontal dashed line either side of the overall pooled effect estimate. * denotes studies that contributed more than one effect size to the meta-analysis.



**Fig 3. Risk of Bias**

The highest bias was consistently identified in domains: protocol registration and sample size calculation.

### BACKGROUND

**Interoception** refers to a system of processes responsible for the perception and integration of internal bodily signals. There is growing interest in the dysregulation of interoception.

**Dysregulated interoception** has been identified in a diverse range of disorders, though most prominently in mental health conditions (Murphy et al., 2021). The direction and consistency of interoceptive dysregulation, and its association with the clinical conditions, is yet to be characterised.

**The heartbeat evoked potential** (HEP) – an event-related-potential time-locked to the R-wave of a heartbeat (Fig 2) – is a neurophysiological marker of interoception (Fig 1). It is understood that a larger HEP amplitude is positively correlated with better interoception (Gentsch et al., 2019).

### AIM

We aimed to determine if a difference in HEP amplitude exists between individuals with a clinical diagnosis and individuals without.

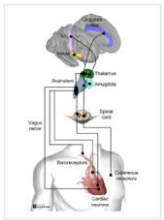



**Fig. 1** ***Park & Blanke, 2019; NeuroImage:*** Multiple physiological pathways involved in cardiac interoception and HEP generation

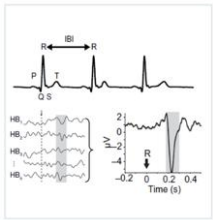



**Fig. 2** ***Azzalini, Rebollo, Tallon-Baudry, 2019; TICS:*** Example of an ECG (Top). Left: Several occurrences of responses to single heartbeats; Right: average HEP

### METHODS

A systematic review and multi-level-meta-analysis was conducted (***osf.io/tmq3w/***) in accordance with the PRISMA guidelines and PICO framework.

**Eligibility**

HEP response to an interoceptive task in a clinical population and a healthy comparison group.

**Databases**

MEDLINE, Cochrane, SCOPUS, Embase, EmCare, PsychINFO, and Web of Science. All reference lists of included studies were manually checked to identify any potentially missed articles.

**Data Extraction**

Group characteristics, task condition, EEG methods, and quantitative outcome data for the HEP response (SMD).

**Risk of Bias**

Customised Risk of Bias (Fig 3) form was developed based on the STROBE checklist (von Elm et al., 2008) and two EEG-specific appraisal guidelines (Keil et al., 2014; Picton et al., 2000). The highest bias was consistently identified in domains: protocol registration and sample size calculation.

### RESULTS

A total of 24 clinical conditions were analysed (SMD = -0.35, SE = 0.2, CI = -0.82 to 0.12, PI = -2.32 to 1.62].

**Neuropsychiatric**

The neuropsychiatric group showed a reduced interoceptive response, as indicated by the small negative effect estimate (SMD = -0.07, SE = 0.08, 95% CI=-0.23 to 0.09, PI = -0.3 to 0.02).

**Neurological**

The neurological group showed a reduced interoceptive response, as indicated by the large negative effect estimate (SMD = -1.18, SE = 0.14, 95% CI = -1.46 to -0.9, PI = -1.4 to -0.78) was found.

**Cardiovascular**

The cardiovascular group showed a reduced interoceptive response, as indicated by the small negative effect estimate (SMD = -0.29, SE = 0.17, 95% CI = -0.62 to 0.04, PI = -0.62 to 0.04) was found.

**Task Condition**

A reduced interoceptive response (SMD = -0.63, SE = 0.09, 95% CI = -0.81 to -0.46) was found for the interoceptive task condition. A small negative effect estimate (SMD = -0.08, SE = 0.09, 95% CI = -0.20 to 0.18) was found for the resting state task condition.

### DISCUSSION

**Diagnostic Condition** subgroup analysis (Table 1) suggests the relationship between interoception and clinical pathologies is not linear; that is, while some conditions are marked by a reduced interoceptive response, others are marked by an enlarged interoceptive response.

**Task Condition** subgroup identified potential clinical utility as HEP was more distinct during active interoceptive tasks (SMD = -0.63), compared to a passive resting state task (SMD = -0.08). These findings indicate interoception varies as a function of clinical and testing condition.

**An overall prediction interval of -2.32 to 1.62 identifies what effect is to be expected in future clinical conditions. However, this review highlights inconsistencies in the HEP methodology that may explain the variability of results, and by extension, limit the potential clinical inferences that can be drawn. A consensus-driven, systematic approach for future HEP research is necessary.**

Murphy et al., 2021 doi 10.1016/j.neubiorev.2021.07.036
Gentsch et al., 2019 doi 10.1002/hbm.24352
Park et al., 2019 doi 10.1016/j.neuroimage.2019.04.061
Azzalini et al., 2019 doi 10.1016/j.tics.2019.03.007
von Elm et al., 2008 doi 10.1016/j.jclinepi.2007.11.008
Keil et al., 2014 doi 10.1111/psyp.12147
Picton et al., 2000 PMID: 10731765

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## 11.5 Poster Presentation – Australian Pain Society Annual Scientific Meeting 2022, Tasmania, Australia.

# SENSING THE BODY IN PAIN:

## Body perception and pain in individuals living with fibromyalgia, complex regional pain syndrome, and chronic musculoskeletal pain


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Pain groups reported higher scores than healthy controls on assessments of body awareness and autonomic reactivity.

There was weak to moderate correlation of these scores with pain severity and interference as assessed by brief pain inventory.

Further studies to investigate the physiological mechanisms that underpin altered body awareness and autonomic reactivity are warranted.

### BACKGROUND

How our body feels is a fundamental component of our sense of self. The biological substrates of body awareness are complex, and include autonomic systems. The role of body awareness and autonomic reactivity has been described across a range of conditions including widespread chronic pain[1] and there is rising interest in relating physiological and neural processes to subjective body experiences and mental health. As such there is a need to investigate subjective body experiences in a way that conceptually links with neuroscience, physiology and medicine. Self report using the **Body Perception Questionnaire** (BPQ)[2] is a validated method to assess the subjective experience of function and reactivity of the structures innervated by the autonomic nervous system and body awareness.

### AIMS

1. To investigate self-reported body perception across chronic pain groups
2. To investigate the correlation between self-reported body perception and pain severity and interference across chronic pain groups

### METHODS

Individuals living with fibromyalgia (FM), complex regional pain syndrome (CR), chronic musculoskeletal pain (CM), or that consider themselves healthy (HC) completed an online survey about demographics, pain history, mood, the BPQ with outcomes 'body awareness' 'supradiaphragmatic reactivity' and subdiaphragmatic reactivity' and the **Brief Pain Inventory** (BPI) with outcomes 'pain severity' and 'pain interference' (results displayed in Table 1 and sample questions from each task displayed in Figure 2).

**Linear model:** Effect of Group, Mood, and Gender on each of the BPQ domains.

**Pearson correlation coefficient:** Relationship between BPQ outcomes and BPI outcomes

### RESULTS

**Aim 1:** People with any chronic pain condition scored higher than HC on all BPQ outcomes. There was an effect of group and mood on BPQ outcomes 'awareness' and 'supradiaphragmatic reactivity' and only of group on 'subdiaphragmatic reactivity'. Age and gender did not have an effect.

**Aim 2:** People with CR and FM scored higher on **body awareness** than either the HC or people with CM. There was no difference between the pain groups for the measure of **supradiaphragmatic reactivity**, but all pain groups scored higher than HC suggesting that respiratory and cardiovascular reactivity is similar between pain groups but differs from healthy controls. There was no difference between the pain groups for the measure of **subdiaphragmatic reactivity**, but all pain groups scored higher than HC, suggesting that gut reactivity is similar between pain groups, but differs from healthy controls.

### CONCLUSION

These results show a higher self-report score on body awareness in chronic pain groups than healthy controls. This is consistent with higher self-report scores of autonomic reactivity in chronic pain groups than healthy controls. Further investigations using physiological correlates of autonomic reactivity to probe the mechanisms that underpin these changes are warranted.

**Table 1** Table of Sample Characteristics

| | Fibromyalgia | Complex Regional Pain Syndrome | Chronic Musculoskeletal Pain | Healthy Control |
|---|---|---|---|---|
| *n* | 81 | 53 | 73 | 55 |
| Mean age (SD) | 42.6 (± 13.2) | 45.21 (± 12.8) | 49.47 (± 17) | 39.69 (± 12.3) |
| Gender | 79F | 47F | 61F | 44F |
| **Body Perception Questionnaire** | | | | |
| Mean Awareness (SD) | 72.77 | 148.74 (42.2) | 62.03 (17.85) | 50.96 (16.5) |
| Mean Supradiaphragmatic (SD) | 32.49 (9.88) | 28.55 (8.66) | 27.81 (9.5) | 21.84 (7.21) |
| Mean Subdiaphragmatic (SD) | 13.21 (3.85) | 12.38 (3.85) | 11.37 (3.65) | 8.86 (2.68) |
| **Brief Pain Inventory** | | | | |
| Mean Severity (SD) | 5.46 (1.5) | 6.23 (1.72) | 4.69 (1.63) | 1.93 (1.81) |
| Mean Interference (SD) | 6.26 (2.1) | 6.43 (2.26) | 4.7 (2.04) | 2.21 (2.43) |

**Fig. 1** Raincloud plot demonstrating the difference in body awareness among different persistent pain conditions

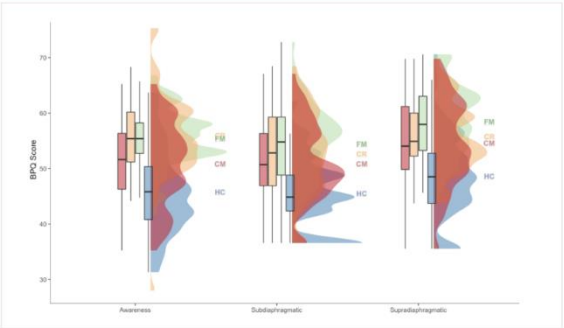



**Fig. 2** Heatmap demonstrating Pearson correlation coefficients between tasks (where darker squares reflect a higher correlation)

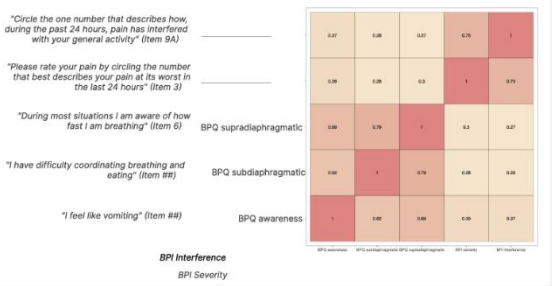
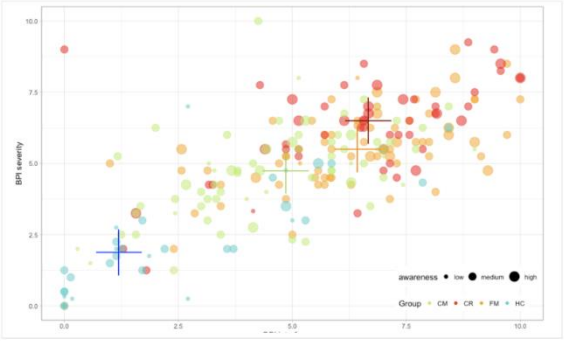



**Table 2** Linear model outcomes

| | Groups | Mean difference | 95% confidence interval | Adjusted *p*-value |
|---|---|---|---|---|
| **Awareness** | CM-HC | 5.05 | 1.82 - 8.27 | **.0004** |
| | CR-HC | 10.17 | 6.7 - 13.65 | **< .0001** |
| | FM-HC | 9.62 | 6.46 - 12.77 | **< .0001** |
| | CR-CM | 5.13 | 1.87 - 8.39 | **.0004** |
| | FM-CM | 4.57 | 1.66 - 7.48 | **.0004** |
| | FM=CR | 0.56 | -3.75 - 2.63 | .9690 |
| **Supradiaphragmatic** | CM-HC | 5.90 | 2.53 - 9.26 | **< .0001** |
| | CR-HC | 7.11 | 3.48 - 10.47 | **< .0001** |
| | FM-HC | 9.78 | 6.48 - 13.07 | **< .0001** |
| | CR=CM | 1.22 | -2.19 - 4.62 | .7923 |
| | FM=CM | 3.88 | 0.84 - 6.92 | .0061 |
| | FM=CR | 3.66 | -0.67 - 5.99 | 1668 |
| **Subdiaphragmatic** | CM-HC | 5.38 | 2.11 - 8.64 | **.0002** |
| | CR-HC | 7.12 | 3.59 - 10.64 | **< .0001** |
| | FM-HC | 8.89 | 5.69 - 12.08 | **< .0001** |
| | CR=CM | 1.74 | -1.56 - 5.04 | .5232 |
| | FM=CM | 3.51 | 0.56 - 6.46 | .0125 |
| | FM=CR | 1.77 | -1.46 - 5 | .4915 |

**Fig. 3** Linear model demonstrating the relationship between pain interference (x-axis) and pain severity (y-axis) from the BPI. Body awareness is demonstrated by the bubble size.





All data and code described in this study are openly available in the Open Science Framework at osf.io/ns2d5/

Licence: CC0 1.0 Universal



[1] Kelaca & Porges., 2018 doi: 10.3389/fnhed.2018.00145

[2] Cabrera et al., 2017 doi: 10.1002/mpr.1596

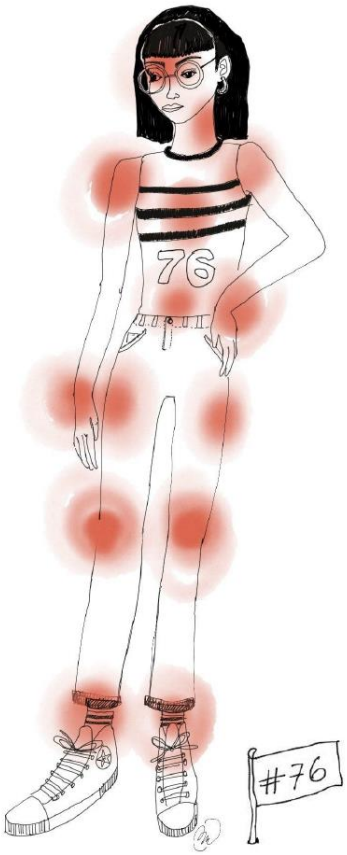


osf.io/ns2d5/

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**11.7 Rapid Talk APS 2022 – Study 2: Most frequently reported areas of pain in people living with fibromyalgia represented on drawing of a woman (Poster # 76)**



## 11.8 Additional activities during candidature

### Professional Development, Community Outreach, and Research Experience

Since 2016, I have been employed as a Research Assistant within the Centre for Cognitive and Systems Neuroscience at the University of South Australia following a voluntary position. Here, I have been responsible for conducting studies that investigate neurophysiological (such as EEG) and neurocognitive measures of brain health (such as participant interview and cognitive assessments). In this role, I have met and worked with approximately 1100 participants. Through this position, I have gained a strong background in the collection and analysis of quantitative and qualitative data.

During my postgraduate studies, I have demonstrated my commitment to community-minded research by engaging in two not-for-profit public outreach and education initiatives; Pain Revolution and Colour the World Orange. As the Evaluation Officer for the Pain Revolution organisation, I was responsible for leading the evaluation team. This involved evaluating three years of data collected across more than 50 events which allowed for outcome comparison across years. Data were evaluated for community events, public seminars, health practitioner workshops, outreach tour feedback, and education program outcomes. The annual outreach tours approximated 1500 attendees, with a 70% feedback completion rate. This role heavily relied on liaising with internal team members and external stakeholders. The valuable feedback from stakeholders (people living with or caring for people with persistent pain, health professionals) was used to make changes to the messaging and approach of the program. In my time, I was able to re-structure and re-design the evaluation process which directly increased the accessibility and ease of providing feedback for stakeholders. This involved assisting in re-developing the program logic that could be adapted to the different programs within Pain Revolution and identify the value and impact of the programs. My time with Pain Revolution concluded when I was awarded the Pain and Interoception (PAIN) Scholarship from the University of South Australia to pursue my Master's by Research full time.

Since 2019, I have maintained voluntary involvement in the annual Colour the World Orange for Complex Regional Pain Syndrome event in Adelaide. Within a small team of four people, my role has focused on promoting awareness of the event in community groups for people living with CRPS, loved ones caring for people with CRPS, and health providers such as nurses, GPs and psychologists that care for people with CRPS. Since my involvement, event attendance has increased 350%. I then went on to chair the 2020 event, a highlight of my involvement. I have now built a network of people who are actively involved in advocating for people with persistent pain conditions, and this has significantly assisted in the recruitment of people in my research studies. In 2023, I began working with MoreGoodDays, a health platform that offers an affordable and accessible evidence-based pain-management program, a multidisciplinary team of health professionals, and a supportive community for individuals living with fibromyalgia. My role involves research evaluation and content writing for the online community.

**Certificates and workshops**

1. Four-Week Workshop: ATN Frontiers Policy and Impact Futures: Understanding Contemporary Policy Making in Practice (06/23)
2. Four-Week Workshop: ATN Frontiers: The Future of Communication (06/23)
3. Satisfactory Working with Children Check (03/23)
4. Satisfactory Police Check (03/23)
5. Certificate of Completion: Mental Health First Aid (04/21)
6. QPR Gatekeeper Training (08/20)
7. Two-Day Workshop: A guided tour of Practical Data Science with R (11/19)

**UniSA Colour the World Orange Annual Event** 2019 - Present

Event organiser, moderator, advertisement designer

**'Nudgeathon' Co-Design Participant** 2022

Developed 'nudges' to increase Influenza and COVID-19 vaccine uptake in pregnant women

**Pain Masterclass by Noigroup** Jun 2021

Communications team member – Involvement in engaging with participants of the masterclass (~700 attendees) over the three days by responding to questions relating to the content of the course, providing referenced literature, and sharing knowledge and experiences in the field of pain research.

**International Interoception Weekly Journal Club – Online** Mar 2020 – Dec 2020

**International ECG Lab Weekly Journal Club – Online** Dec 2020 – Mar 2021

**UniSA Colour the World Orange Event – Online** Nov 2020

Event moderator and organiser - Involvement in the organisation of the first virtual event in SA which required a restructure of the general program and presentation.

**UniSA Colour the World Orange Event – UniSA City East** Nov 2019

Involvement in the organisation of the free event raising awareness for Complex Regional Pain Syndrome (CRPS)
Independently designed poster to promote attendance, created and maintained webpage which saw the increase of attendance from 50 in 2018 to over 150 in 2019.

**Memberships**

Australasian Cognitive Neuroscience Society 2022

Australian Pain Society 2019 – 2023

International Association for the Study of Pain 2021

Australasian Cognitive Neuroscience Society 2017 – 2019

**Scholarships**

Postgraduate Award in Interoception (PAIN) scholarship 2020 – Current

Commonwealth Government fee waiver scholarship 2019 – Current

**Employment**

**University of South Australia**

**University of South Australia Online** Feb 2022 – Current

Online Tutor & Assessment Marking

Psychology 1B *(Dr Fernando Marmolejo-Ramos)*

Aboriginal Australians and Psychology *(Dr Shelly Belmont)*

Personal and Professional Development *(Dr Fernando Marmolejo-Ramos)*

Workplace and Organisational Psychology *(Dr Fernando Marmolejo-Ramos)*

**UniSA Centre for Cognitive and Systems Neuroscience** May 2017 – Jan 2023

Research Assistant *(Prof Ina Bornkessel-Schlesewsky)*

Conduct research experiments that use electroencephalography and behavioural measures

Data entry and management of information pertaining to study participants in a confidential and professional manner

Experimental creation and conceptualisation

Collaboration with researchers on writing research articles

**University of Adelaide**

**Adelaide University School of Psychology** Apr 2021 – Current

Research Assistant *(Dr Conrad Perry)*

Conduct research experiments that use electroencephalography

Tutoring

*Psychology 1A* - Dr Rachel Stephens Mar-Jun 2022

Assessment Grading

*Psychology 1A* - Dr Rachel Stephens

*Perception and Cognition* - Dr Mark Kohler

*Individual Differences, Personality & Assessment* - Dr Conrad Perry

**Pain Revolution Outreach Program** Sep 2019 – Feb 2020

Research Assistant and Evaluation Officer *(Prof Lorimer Moseley)*

Evaluation of 3 years of data collected from ~ 1500 attendees across more than 50 community events (public seminars, health practitioner workshops, outreach tour feedback, and education program outcomes)

Data entry and analysis, thematic analysis, and evaluation reporting of events

Re-development of the evaluation structure and program logic

Follow-up and correspondence with health practitioners involved in the education program

**Conference Attendance**

| | |
|---|---|
| **Australian Social and Affective Neuroscience Conference - Sydney** | June 2022 |
| **Australian Pain Society Annual Scientific Meeting – Tasmania** | April 2022 |
| **World Congress on Pain - Online** | 9-11, 16-18 Jun 2021 |
| **Australian Pain Society Annual Scientific Meeting – Online** | 19-20 Apr 2021 |
| Mind Body Brain Symposium - Online | Mar 15 - 18 2021 |
| Adelaide Sleep Retreat - Adelaide | Nov 12 2020 |
| Neuromatch 3.0 - Online | Oct 26 - 30 2020 |
| **CRPS Awareness Night - Online** | Nov 2 2020 |
| Pain Society of Alberta Conference - Online | Oct 16 - 18 2020 |
| The Fibro Summit - Online | Sep 28 - Oct 4 2020 |
| Computational Psychiatry Course - Online | Sep 7 - 12 2020 |
| Reading Emotions | Jun 11 - 12 2020 |
| NeuroMatch Academy: Computational Neuroscience Training - Online | Jul 13 - 21 2020 |
| Experimental Psychology Society Conference - Online | Jul 2 2020 |
| Human Brain Mapping: Reproducibility Crisis Webinar - Online | May 26 2020 |
| **Australian Pain Society Poster Gala - Online** | May 2020 |
| CRPS Awareness Night - Adelaide | Nov 2019 |
| Pain Adelaide Conference - Adelaide | Mar 2019 |
| ACNS Conference - Melbourne | Nov 2018 |
| CRPS Awareness Night - Adelaide | Nov 2018 |
| **ACNS Conference - Adelaide** | Nov 2017 |

*Bold denotes attendance and participation (presentation/poster/chair/rapid talk)*