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Cardiac interoception in patients accessing secondary mental health services: A transdiagnostic study

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\textbf{A R T I C L E   I N F O}

\textbf{Keywords:} Anxiety, Interoception, Cardiac physiology, Psychosis, Transdiagnostic

\textbf{A B S T R A C T}

\textbf{Background:} Abnormalities in the regulation of physiological arousal and interoceptive processing are implicated in the expression and maintenance of specific psychiatric conditions and symptoms. We undertook a cross-sectional characterisation of patients accessing secondary mental health services, recording measures relating to cardiac physiology and interoception, to understand how physiological state and interoceptive ability relate transdiagnostically to affective symptoms.

\textbf{Methods:} Participants were patients (n = 258) and a non-clinical comparison group (n = 67). Clinical diagnoses spanned affective disorders, complex personality presentations and psychoses. We first tested for differences between patient and non-clinical participants in terms of cardiac physiology and interoceptive ability, considering interoceptive tasks and a self-report measure. We then tested for correlations between cardiac and interoceptive measures and affective symptoms. Lastly, we explored group differences across recorded clinical diagnoses.

\textbf{Results:} Patients exhibited lower performance accuracy and confidence in heartbeat discrimination and lower heartbeat tracking confidence relative to comparisons. In patients, greater anxiety and depression predicted greater self-reported interoceptive sensibility and a greater mismatch between performance accuracy and sensibility. This effect was not observed in comparison participants. Significant differences between patient groups were observed for heart rate variability (HRV) although post hoc differences were not significant after correction for multiple comparisons. Finally, accuracy in heartbeat tracking was significantly lower in schizophrenia compared to other diagnostic groups.

\textbf{Conclusions:} The multilevel characterisation presented here identified certain physiological and interoceptive differences associated with psychiatric symptoms and diagnoses. The clinical stratification and therapeutic targeting of interoceptive mechanisms is therefore of potential value in treating certain psychiatric conditions.

Our understanding of psychiatric conditions is often dominated by either neurochemical or psychological models; a dichotomy reflected in current treatments. However, more integrative approaches are emerging with increasing attention to the role of the body and the processing of bodily states in psychological health (Critchley and Harrison, 2013; Khalsa et al., 2018; Quadt et al., 2018; Tsakiris and Critchley, 2016). Interoception refers to the signalling, processing and representation of internal bodily states by the central nervous system (Khalsa et al., 2018). Physiologically, interoceptive signalling is involved in coordinating homeostatic reflexes (e.g., control of blood pressure or glucose levels

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with a set range) and by guiding predictive (allostatic) autonomic and behavioural responses (e.g., preparing the body for action by increasing blood pressure and heart rate). Psychologically, interoceptive representations are proposed to underpin both motivational (e.g., hunger) and emotional (e.g., anxiety) feeling states (Craig, 2002; Critchley and Garfinkel, 2017; Critchley et al., 2004; Garfinkel et al., 2015a; Strigo and Craig, 2016). By extension, autonomic control and interoceptive signalling are implicated in the physical consequences of psychological challenges (e.g., stress-related cardiovascular morbidity) as well as in the psychological symptoms linked to poor physical health or allostatic overload (Bell et al., 2017; Critchley and Harrison, 2013; Krishnasadas and Harrison, 2016; Lane et al., 2009).

Within psychiatry, as a basis of motivational drive and representations of bodily integrity, interoception is arguably in the foreground of eating disorders (Kaye et al., 2009; Khalsa et al., 2015), addiction (Paulus and Stewart, 2014; Stewart et al., 2020) and somatization (Flasinski et al., 2020; Sugawara et al., 2020). Reflecting the link with emotional feelings, interoceptive processes are also implicated in the expression of mood and anxiety symptoms (Critchley and Harrison, 2013; Khalsa et al., 2018; Tsakiris and Critchley, 2016). Moreover, in contemporary models of consciousness, by supporting a coherent continuity of subjective self-experience, interoception is proposed to be fundamental to self-representation (or ‘biological self’) (Lane et al., 2009; Seth and Tsakiris, 2018; Suzuki et al., 2013; Tsakiris et al., 2011).

Disrupted interoceptive functioning may thus manifest as disturbances of conscious selfhood, e.g., as symptoms of dissociation, depersonalisation, and related psychotic phenomena (Ardizzi et al., 2016; Eccles et al., 2015; Quadt et al., 2018; Schäfflein et al., 2018). If interoception is indeed central to psychological health, we need to understand its contributions to mental health conditions. Both the Research Domain Criteria initiative (RDc) of the National Institute of Mental Health (USA) and the Hierarchal Taxonomy of Psychopathology (HiTOP) have proposed transdiagnostic biological taxonomies for mental illness, with a view toward better treatment targets. RDc’s major functional domains are negative valence, positive/reward valence, cognitive systems, systems for social processes (including self-representation) and arousal/modulatory systems (Insel et al., 2010). HiTOP’s major functional domains include somatoform (bodily symptoms), internalizing (emotional lability), thought disorder (e.g., unusual beliefs or experiences), detachment (emotional detachment), disinhibited externalizing (impulsivity), and antagonistic externalizing (antisocial behaviour) (Conway et al., 2019).

Interoceptive processing is arguably present across numerous domains within each of these taxonomies, representing a more fundamental construct that supports basic physiological regulation, motivation, emotional feelings, and self-representation. Here, we tested how accessible indices of physiological regulation (heart rate and heart rate variability) and aspects of interoception (heartbeat detection and self-reported sensitivity to bodily signals) relate to presentation, affective symptoms and diagnosis in patients accessing secondary psychiatric services.

Interoceptive signals are generated throughout the body via mechanoceptor and chemoreceptor activation of afferent pathways (Critchley and Garfinkel, 2017). Perceptual characteristics of interoceptive sensations are distinguished by afferent channel and signal strength. Signals are projected throughout the neuraxis (including the autonomic ganglia, spinal cord, medulla, pons hypothalamus, thalamus, basal ganglia, amygdala and hippocampus) via spinal and cranial nerves towards the hypothalamus and hypothalamic centre (Critchley and Harrison, 2013). Representations in these brain areas are believed to contribute to the direction of adaptive behaviour (Kleckner et al., 2017). Importantly, altered activity in the insula is a transdiagnostic predictor of interoceptive dysfunction (Nord et al., 2021).

Despite the influence of interoceptive information throughout the body, a majority of literature to date has focused on cardiac signals. In particular, the baroreflex which maintains blood pressure through baroreceptor activation during cardiac systole produces interoceptive information in the form of heartbeat strength and timing and is strongly associated with heart rate variability (HRV) (Critchley and Harrison, 2013). Greater HRV is linked to improved health outcomes, including cognitive flexibility and emotion regulation (Forté et al., 2019). Measured as the change in cardiac inter-beat intervals over time, it is an important feature of a dynamic and adaptive autonomic system, allowing for rapid anticipation, mitigation and response to changing environmental demands (Mulcahy et al., 2019).

People often vary in how precisely they consciously perceive internal bodily sensations. Greater sensitivity to interoceptive feelings (measurable using questionnaires or behavioural tasks) may predict stronger emotional experiences. For example, interoceptive sensitivity—including both behavioural accuracy and self-report sensitivity—is reportedly higher among anxiety and panic patients, but lower in depression (Dunn et al., 2010a; Garfinkel et al., 2015b; Van der Does et al., 1997; Zoellner and Crabbe, 1999). Interoceptive differences are also associated with psychotic symptoms in schizophrenia (Ardizzi et al., 2016; Schäfflein et al., 2018). On their own, such findings are heuristic due to psychometric limitations of interoceptive tasks (Brener and Ring, 2016; Corneille et al., 2020). Improving upon this, one influential framework distinguishes among the following interoceptive dimensions: self-report (questionnaire/confidence ratings), behavioural accuracy (performance accuracy on interoceptive tasks, e.g., heartbeat detection), and insight (a metacognitive measure detailing the correspondence between behavioural and self-report measures) (Garfinkel et al., 2015b; Khalsa et al., 2018). Discrepancy between self-report and behavioural accuracy measures of interoception may account for affective symptoms, and is a promising target for intervention (Garfinkel et al., 2015b; Garfinkel et al., 2016). In a randomized controlled trial, training to enhance behavioural accuracy on cardiac interoception tasks decreased anxiety in autistic adults significantly more than an active control intervention (Quadt et al., 2021). Interoceptive abilities also predict intuitive decision-making (Dunn et al., 2010a), a ‘stronger representation of self’ (Tsakiris et al., 2011), and enhanced impulse control (Herman et al., 2019), linking predictive interoceptive representations to self-regulation (Eccles et al., 2015; Quadt et al., 2018; Seth and Tsakiris, 2018; Suzuki et al., 2013; Tsakiris et al., 2011).

The relevance of interoception to mental health goes far beyond the narrow view that it is primarily concerned with perception of visceral changes and performance accuracy on heartbeat detection (or related) tasks to encompass homeostatic and allostatic control, motivational drive, hormonal, metabolic, immune and gut-brain influences on mind and behaviour. Nevertheless, sensitivity to, and interpretation of, internal physiological responses remains relevant to certain patient groups. Importantly, in this context, the value of performance in the (easy-to-implement) heartbeat tracking task for understanding interoceptive influences (‘baseline/threshold’ individual differences) on psychopathology has been called into question many times, most recently in a meta-analysis (Desmedt et al., 2022). Therefore, the present study, measuring cardiac interoception via two heartbeat detection tasks in patients accessing generic secondary mental health services, makes an important and timely contribution.

With converging evidence now connecting psychological symptom expression to aspects of cardiac interoception, there is a need for systematic characterisation in clinical patients (Khalsa et al., 2018). Here we explored associations between measures of cardiac physiology and interoception and affective symptoms (depression and anxiety) in a group of representative patient and comparison participants.

1. Materials and methods
1.1. Research ethics, governance and study sample

The study was approved by the National Research Ethics Service (13/LO/1866MHRNA), and registered with the International Standard Randomized Controlled Trial Registry (ISRCTN13588109). Patients at
least 18 years of age and accessing services for a recorded psychiatric diagnosis were recruited from secondary care mental health clinics, or self-referred from advertisement in primary care and community settings. The study was conducted between 2014 and 2019. Exclusion criteria included global cognitive impairment, neurological conditions, and alcohol intake on day of testing. Clinical diagnoses by psychiatrists were confirmed from medical records. An anxiety group, comprising generalised anxiety, social anxiety and panic disorder, was distinguished from posttraumatic stress, and obsessive-compulsive disorders (PTSD, OCD). In addition, patients with schizophrenia or paranoid schizophrenia were categorised separately from patients with schizoaffective disorder, psychosis with affective features, or unspecified psychosis.

Comparison participants, eligible adults with no formal mental health diagnosis were recruited through poster advertisements. Exclusion criteria were history of mental or systemic medical illness and medication affecting cardiovascular or cognitive function. Assessments took place in university facilities and hospital clinic rooms.

1.2. Assessment of cardiac physiology and interoceptive dimensions

Heart Rate and Heart Rate Variability. Medical-grade pulse oximetry (Nonsin Xp®; 3012LP with soft finger-mount (Murphy et al., 2019) was used to record heart rate and measure heart rate variability (HRV). Pulse oximetry measures differences in light absorption of blood, based on oxygen levels. Each heartbeat sends oxygenated blood to the body, increasing the oxygen saturation signal at the finger. At rest, this produces an oscillatory signal with the same temporal resolution as the electrocardiogram (ECG) signal (Iyriboz et al., 1991; Murphy et al., 2019). Heart rate (measured as pulse rate) was averaged over the six trials of the heartbeat tracking task (Murphy et al., 2019; see below). HRV was computed as the root mean square of successive differences between pulses (RMSSD) (Munoz et al., 2015) during concatenated trials of the heartbeat tracking task (see below). Thus, the overall length of time used to determine HRV was 225 s.

Heartbeat Tracking Task (Schanzky, 1981). Participants were asked to report the number of perceived heartbeats at rest over six randomized trials of length 25, 30, 35, 40, 45 and 50 s. Immediately after each trial, they rated their confidence in the accuracy of their response on a continuous visual analogue scale (VAS) ranging from 0 cm (“Total guess/No heartbeat awareness”) to 10 cm (“Complete confidence/Full perception of heartbeat”). Behavioural accuracy was quantified by comparing the number of reported heartbeats to recorded pulses via the following: 1 – [(nbeatsrecorded – nbeatsportal)/(nbeatsrecorded + nbeatsportal)]/2 (Garfinkel et al., 2015b). Scores were averaged across the six trials to produce a single accuracy and confidence value for each participant. Metacognitive insight (awareness) was computed as the Pearson correlation between accuracy and confidence values across trials (Garfinkel et al., 2015b).

Heartbeat Discrimination Task (Katkin et al., 2001; Whitehead et al., 1977; Wiens and Palmer, 2001). Each trial consisted of 10 auditory tones (440 Hz for 100 ms) presented either synchronously or asynchronously (delayed) relative to heartbeats. Synchronous tones were trigged at the rising edge of the pulse pressure wave. Asynchronous tones were presented after a 300 ms delay. Thus, adjusting for the average 250 ms delay between the ECG R-wave and arrival of the pressure wave at the finger (Payne et al., 2006), tones were delivered around 250 ms or 550 ms after the R-wave, corresponding to maximum and minimum synchronicity judgements, respectively (Wiens and Palmer, 2001). After each trial, participants judged if tones were synchronous or asynchronous relative to their heartbeats, then rated their confidence in the accuracy of their judgement on a continuous VAS ranging from 0 cm (“Total guess/No heartbeat awareness”) to 10 cm (“Complete confidence/Full perception of heartbeat”). They completed 40 trials over two sessions. Accuracy was calculated as the number of correct trials divided by the total number of trials (i.e. the proportion of correct trials). Confidence scores were averaged across trials to produce a single value. Metacognitive insight (awareness) was calculated as the area under the receiver operating characteristic (ROC) curve relating accuracy and confidence scores across trials (Garfinkel et al., 2015b).

Porges Body Perception Questionnaire (BPQ) (Cabrera et al., 2018; Porges, 1993) and Interoceptive Trait Prediction Error. Self-report interoceptive ‘sensibility’ was quantified from self-rating sensitivity to bodily sensations on the BPQ-awareness subscale. Interoceptive Trait Prediction Error (ITPE) (Garfinkel et al., 2016) quantified ‘interoceptive surprise’ from discrepancy (on the z-score scale) between self-report (BPQ-awareness score) and behavioural (heartbeat tracking/discrimination accuracy) interoceptive measures (Garfinkel et al., 2016).

1.3. Assessment of affective symptoms

 Beck Depression Inventory (BDI) (Beck et al., 1961). This is a 21-question self-report scale of symptoms associated with depression, e.g., level of feelings of worry, failure and disappointment. Scores are measured on a 4-point scale (0–3) with higher scores indicating more severity. Total scores have a maximum of 63 points. The BDI demonstrates high internal consistency and has alpha coefficients of 0.86 and 0.81 for psychiatric and non-psychiatric populations respectively (Beck et al., 1988).

 State-Trait Anxiety Inventory (STAI) (Spielberger, 1983). This is a 40-item self-report questionnaire measuring state (STAI-Y1; 20 items) and trait anxiety (STAI-Y2; 20 items). State anxiety measures in the moment positive and negative conditions such as feeling upset and feeling comfortable. Trait anxiety is measured using items relating to general personal tendencies, e.g., feeling calm, cool and collected or feeling that difficulties are piling up and cannot be overcome. A 4-point scale (from “Almost Never” to “Almost Always”) is used to rate all items and higher scores indicate greater anxiety. Total scores have a maximum of 80 points. The scale’s internal consistency coefficients range from 0.86 to 0.95 (Spielberger, 1983).

1.4. Statistical analyses

Descriptive summaries of participant characteristics and baseline physiological, interoceptive and affect scores were carried out for each group (patients, comparison participants) and for all participants (patients + comparisons). Counts (n), percentages (%), mean (m) and standard deviations (±SD) were used. Participant characteristics included age, sex, Body Mass Index (BMI), and medication use indicated by antipsychotics (no/yes) and antidepressants (no/yes). Differences in patient characteristics were tested using Chi-Square or Fisher’s Exact tests for categorical variables and Analysis of Variance (ANOVA) for continuous variables.

1.4.1. Between group differences on cardiac physiology and interoceptive dimensions

Between-group analyses were conducted using ANOVAs. Initial analyses compared patient with comparison participants on cardiac physiology and interoceptive dimensions. A second exploratory analysis looked at the effect of medication on the patient group by comparing participants using antipsychotics and/or antidepressants to those not using medication. A third analysis explored differences between patient diagnostic groups. To maintain the robustness of our comparisons, diagnostic groups with very small numbers (i.e., n < 10 were excluded from this subgroup analysis) as was the complex diagnostic category (see below) due to the inconclusive and heterogeneous nature of the group.

1.4.2. Correlations between interoceptive and affective symptoms

Spearman’s rank correlations, ρ(n), were used to test for relationships between physiological/interoceptive measures and affective symptoms in patient and comparison participants separately.

Each of the above analyses were repeated with age, sex and BMI included simultaneously to consider their potential effect as
confounding covariates on physiology and interoception. This had the aim of increasing inferential precision and group balance on baseline factors. We did not impute for missing values present across the dataset. For all statistical tests, an alpha level of 0.05 was used.

2. Results

2.1. Participant characteristics, baseline physiology and affect

A total of 67 (17.9 %) comparison and 307 (82.1 %) patient participants were recruited to the study giving a grand total of 374 study participants. Comparison participants were aged 18–67 years, and patient participants were aged 18–65 years. Table 1A shows the participant characteristics and baseline scores. Patient diagnoses were depression (n = 59), generalised anxiety, social anxiety and phobic disorder (Anxiety, n = 29); dual diagnosis of schizoaffective disorder, affective psychosis or unspecified psychosis (Schizoaffective, n = 26); obsessive compulsive and unstated conditions (n = 4); Post Traumatic Stress Disorder (EUPD, n = 19); schizophrenia or paranoid schizophrenia (Schizophrenia, n = 19); diagnosis of schizoaffective disorder, affective psychosis or unspecified psychosis (Schizoaffective, n = 26); Obsessive Compulsive Disorder (n = 9); Autistic Spectrum Conditions (n = 6); Attention Deficit Hyperactivity Disorder (n = 4) and Complex inconclusive and unstaTed conditions (n = 16). Categories with n < 10 patients were excluded from between diagnostic group analyses and summary tables but were included in the total patient count. Patients were overall older (patient vs comparison participants, years mean ± SD: 38.9 ± 14.1 vs 35.0 ± 13.2, [F(1, 368) = 4.1, p = .041] with greater BMI (kg/m²) 26.4 ± 7.1 vs 23.0 ± 3.6, [F(1, 336) = 9.2, p = .003]). Of patients, 58 % (n = 176) were female, and 61 % of comparison participants (n = 41) were female; this was not a statistically significant difference (p = .79). Just under two-thirds (65.4 %) of patients took antipsychotic or antidepressant medication; no comparison participants were using medication.

2.2. Differences between patient and comparison participants on cardiac physiological and interoceptive dimensions

Distributions of heart rate and HRV are shown in Fig. 1A-B and Table 1A. ANOVA results are displayed in Table 2. Overall, patients did not differ from comparison participants in heart rate but had lower HRV (patient vs comparison participants, ms: 51.6 ± 42.6 vs 70.8 ± 58.4; p = .003; Fig 1B). However, this difference became non-significant when age, sex, and BMI were included as confounding covariates.

On the heartbeat tracking task, patients were significantly less confident than comparison participants (VAS 4.2 ± 2.6 vs 5.4 ± 1.9; p = .003; with covariates p = .001; see Fig. 2B and Table 2). There was also a significant group difference in performance accuracy (0.48 ± 0.37 vs 0.59 ± 0.3; p = .022; Fig. 2A) which became non-significant (p = .823) after adjustment. However, there was no group difference for metacognitive insight (Fig. 2C).

On the heartbeat discrimination task, patients again showed lower confidence than comparison participants (patient vs comparison participants VAS 5.0 ± 2.4 vs 5.9 ± 1.8; p = .02), even after covariate adjustment (p = .01) (see Fig. 2E and Table 2). Patients’ performance accuracy was also lower (patient vs comparison participants 0.52 ± 0.1 vs 0.57 ± 0.2; p = .03), even with covariate inclusion (p = .03; Fig 2D). Again, groups did not differ in metacognitive insight on this task (Fig. 2F).

Self-rated interoceptive sensibility (BPQ-awareness) did not distinguish patient from comparison participants (112.2 ± 29 vs 114.5 ± 34; p = .64; Fig. 3A). Similarly, there were no group differences in interoceptive trait prediction error, for either the heartbeat tracking (ITPE HBT: 0.04 ± 1.5 vs 0.09 ± 1.4; p = .865; Fig. 3B) or the heartbeat discrimination tasks (ITPE HBD: 0.01 ± 1.4 vs –0.23 ± 1.5; p = .32; Fig. 3C). Thus, patients showed reduced confidence and accuracy in judging their own cardiac sensations relative to comparison participants. These effects were not primarily attributable to differences between patient and comparison participants in physiology (HR or HRV), interoceptive sensibility (BPQ-awareness), metacognitive insight, or

Table 1A
Descriptive summary of participant characteristics and baseline scores.

<table>
<thead>
<tr>
<th>Diagnosis (Max n)</th>
<th>Sex</th>
<th>Sex [%]</th>
<th>Age [yrs]</th>
<th>BMI [kg/m²]</th>
<th>HR [bpm]</th>
<th>HRV [ms]</th>
<th>BDI</th>
<th>STAI-Y1</th>
<th>STAI-Y2</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (Comparison)</td>
<td>41F</td>
<td>61.2</td>
<td>35.0</td>
<td>22.97</td>
<td>70.55</td>
<td>70.82</td>
<td>7.58 (6.1)</td>
<td>29.88</td>
<td>36.92</td>
</tr>
<tr>
<td>(67) Depression</td>
<td>26M</td>
<td>36.8</td>
<td>(13.2)</td>
<td>(3.6)</td>
<td>(8.9)</td>
<td>(58.4)</td>
<td>43</td>
<td>(7.5)</td>
<td>65</td>
</tr>
<tr>
<td>(59) Anxiety</td>
<td>24M</td>
<td>40.7</td>
<td>(15.3)</td>
<td>(7.1)</td>
<td>(11.6)</td>
<td>(45.9)</td>
<td>(13.6)</td>
<td>(10.5)</td>
<td>(11.8)</td>
</tr>
<tr>
<td>(29) Mixed A/D</td>
<td>1NB</td>
<td>1.7</td>
<td>59</td>
<td>59</td>
<td>57</td>
<td>58</td>
<td>59</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>(47) Bipolar</td>
<td>32F</td>
<td>68.1</td>
<td>41.6</td>
<td>25.25</td>
<td>72.83</td>
<td>56.90</td>
<td>27.78</td>
<td>44.40</td>
<td>60.87</td>
</tr>
<tr>
<td>(56) EUPD</td>
<td>31.9</td>
<td>(12.7)</td>
<td>(5.5)</td>
<td>(14.1)</td>
<td>(46.9)</td>
<td>(13.4)</td>
<td>(11.3)</td>
<td>(8.8)</td>
<td></td>
</tr>
<tr>
<td>(22) Schizoaffective</td>
<td>32F</td>
<td>57.1</td>
<td>42.8</td>
<td>27.23</td>
<td>73.85</td>
<td>38.99</td>
<td>22.44</td>
<td>38.43</td>
<td>53.96</td>
</tr>
<tr>
<td>(6) Schizophrenia</td>
<td>24M</td>
<td>42.9</td>
<td>(12.7)</td>
<td>(5.9)</td>
<td>(12.1)</td>
<td>(25.8)</td>
<td>(15.1)</td>
<td>(13.9)</td>
<td>(13.8)</td>
</tr>
<tr>
<td>(13M Mixed A/D)</td>
<td>31.8</td>
<td>(13.1)</td>
<td>(11.4)</td>
<td>(13.7)</td>
<td>(27.0)</td>
<td>(16.8)</td>
<td>(13.2)</td>
<td>(11.5)</td>
<td></td>
</tr>
<tr>
<td>(26) Depression</td>
<td>46.2</td>
<td>20.0</td>
<td>29.92</td>
<td>71.26</td>
<td>40.37</td>
<td>17.61</td>
<td>38.12</td>
<td>50.42</td>
<td></td>
</tr>
<tr>
<td>(12M Schizophrenia)</td>
<td>31.6</td>
<td>40.9</td>
<td>30.35</td>
<td>75.85</td>
<td>35.88</td>
<td>14.78</td>
<td>37.47</td>
<td>43.26</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Data are mean, (SD), n = number of observations. Max n = maximum number in group. F = Female, M = Male, NB = non-binary, # = number, % = percentage, yrs. = years, kg = kilograms, bpm = beats-per-minute; ms = milliseconds; BMI = body mass index; HR = heart rate; HRV = heart rate variability; BDI = Beck Depression Inventory; STAI = Spielberger State and Trait Anxiety Inventory; Y1 = state, Y2 = trait.

* Missing data.
interoceptive trait prediction error.

2.3. Correlations between cardiac physiology/interoceptive and affective symptoms

Patient depression (BDI) and state and trait anxiety scores (Fig. 4) were tested for correlations with cardiac physiology and interoception measures (Table 3). Select correlations are shown in Fig. 5. Depression symptoms were moderately to strongly associated with anxiety (STAI-Y1: \( \rho = 0.52, p < .01 \); STAI-Y2: \( \rho = 0.75, p < .01 \)) and weakly associated with both increased interoceptive sensibility (BPQ-awareness: \( \rho = 0.35, p < .01 \)) and increased interoceptive trait prediction error (ITPE HBT: \( \rho = 0.24, p < .01 \); ITPE HBD: \( \rho = 0.16, p < .01 \)).

Similar to depression symptoms, anxiety symptoms were strongly associated with each other (\( \rho = 0.64, p < .01 \)) and weakly associated with both increased interoceptive sensibility and increased interoceptive trait prediction error. Trait anxiety was also weakly associated with metacognitive insight in heartbeat discrimination (STAI-Y2: \( \rho = 0.19, p < .01 \)). We found no associations between affective symptoms and either physiology or heartbeat detection performance accuracy in patient participants.

To determine if relationships between affective symptoms and cardiac physiology/interoception existed for comparison participants, we again tested for correlations among these data. Here, depression symptoms were only significantly correlated with state anxiety after covariate inclusion (STAI-Y1: \( \rho = 0.279, p = .07 \) vs \( \rho = 0.424, p < .01 \)). They were also moderately correlated with trait anxiety (STAI-Y2: \( \rho = 0.355, p < .001 \)). However, depression symptoms were not associated with cardiac physiology or interoception measures in comparison participants.

Anxiety symptoms in comparison participants were moderately associated with each other (\( \rho = 0.579, p < .001 \)), and state anxiety was moderately associated with decreased self-report confidence in heartbeat discrimination performance (STAI-Y1: \( \rho = -0.324, p = .034 \)). State anxiety was also moderately correlated with heart rate (STAI-Y1: \( \rho = 0.302, p = .049 \)), but this relationship was lost after covariate adjustment (\( \rho = 0.08, p = .63 \)). Thus, in comparison participants only state anxiety was associated with confidence in heartbeat discrimination such that lesser anxiety predicted greater confidence. Otherwise, anxiety symptoms did not relate to cardiac physiology or interoception measures.

2.4. Medication effects

We tested for differences in patients’ physiological and interoceptive measures between those who were using antipsychotic medication only (\( n = 59; 20 \% \)) or not, those using antidepressants only (\( n = 75; 25 \% \)) or not, and those using both antidepressants and antipsychotics (\( n = 58, 20 \% \)) or not. Just over a third (\( n = 102; 35 \% \)) of patients were not using either. Significant findings were limited to: (1) Marginally higher heart rate in people on both antidepressants and antipsychotics, (both vs neither; bpm 77.6 ± 12.7 vs 72.1 ± 10.9 [\( F(1, 275) = 10.4, p = .001 \)]; with covariates \( F(1, 260) = 8.57, p = .004 \)); (2) Significantly higher HRV in patients on antidepressants only (RMSSD: ms: 37.4 ± 48.1 vs 38.3 ± 48.1 [\( F(1, 275) = 7.9, p = .008 \) with covariates \( F(1, 253 = 8.02, p = .005) \)]; and (3) Significantly lower HRV in patients on both antidepressants and antipsychotics (RMSSD: ms: 37.4 ± 26.5 vs 55.7 ± 44.7 [\( F(1, 267) = 7.9, p = .01 \), with covariates \( F(1, 253 = 6.6, p = .011) \)]).

2.5. Differences between patient diagnostic groups on cardiac and interoceptive measures

We tested for differences in physiological and interoceptive measures between groups of patients categorised according to recorded clinical diagnoses. Diagnostic groups explored were depression (\( n = 59 \)), anxiety disorder (\( n = 29 \)), mixed anxiety & depression (\( n = 47 \), bipolar disorder (\( n = 56 \)), emotionally unstable/borderline personality disorder (\( n = 22 \)), schizoaffective disorder (\( n = 26 \)) and schizophrenia (\( n = 19 \)) (see Methods and Tables 1A and 1B).

Distributions of cardiac and interoceptive measures by diagnostic group are shown alongside the comparison group for visual comparison only in Figs. 1, 3, and 6. ANOVAs indicated that among patients there were statistically significant between-group differences in HRV [\( F(6, 228) = 3.3, p = .004 \) with covariates \( F(6, 217) = 2.4, p = .03 \)]. No post-hoc results were significant after Tukey multiple comparison correction.
when considering covariates, although differences between anxiety and bipolar groups and between anxiety and emotionally unstable/borderline groups trended toward significance ($p = .067$ and $p = .096$, respectively). In general, decreased HRV characterised patients with diagnoses of bipolar disorder, emotionally unstable/borderline personality disorder, schizoaffective disorder, and schizophrenia, relative to anxiety and depression groups (and comparison group; Table 1A, Fig. 1D).

Groups differed in behavioural performance accuracy on the heartbeat tracking task [$F(6, 235) = 2.8$, $p = .01$; after covariate inclusion $F(6, 223) = 2.2$, $p = .04$]. This effect was primarily driven by schizophrenia patients exhibiting lower scores (Table 1B, Fig. 6A). Post-hoc Tukey’s tests for multiple comparisons found that the mean accuracy score was different between depression and schizophrenia groups ($p = .030$; 95% CI = [0.018, 0.643]), between mixed anxiety/depression and schizophrenia groups ($p = .018$; 95% CI = [0.037, 0.692]), and between bipolar and schizophrenia groups ($p = .049$; 95% CI = [4.1 × 10$^{-4}$, 0.620]).

Groups also differed in self-report interoceptive sensibility (BPQ-awareness, $F(6, 230) = 2.4$, $p = .03$), although significance was lost after covariate adjustment ($F(6, 219) = 1.78$, $p = .10$). This effect was primarily driven by schizoaffective patients exhibiting lower sensibility (BPQ-awareness) scores compared to mixed anxiety/depression patients ($96.6 \pm 22.3$ vs $119.3 \pm 28.3$, $t(65) = 3.18$, $p_{	ext{tukey}} = 0.027$) and EUPD patients ($96.6 \pm 22.3$ vs $121.8 \pm 28.6$, $t(44) = 3.01$, $p_{	ext{tukey}} = 0.046$; Table 1B, Fig. 3D). A separate t-test revealed that schizoaffective patients also exhibited lower sensibility compared to schizophrenia patients ($96.6 \pm 22.3$ vs $112.9 \pm 22.2$, $t(40) = 2.33$, $p = .025$). Relatedly,
groups also differed in interoceptive trait prediction error on the heartbeat tracking task (F(6, 218) = 2.6, p = .02), but again this difference was not significant after covariate consideration (F(6, 207) = 1.96, p = .07). This effect was primarily driven by schizophrenia patients exhibiting greater interoceptive trait prediction error on the task compared to schizoaffective patients (0.9 ± 1.3 vs –0.6 ± 1.1, t(36) = 3.24, p_{tukey} = 0.023; Table 1B, Fig. 3E). Self-reported confidence in heartbeat detection performance and metacognitive interoceptive awareness of heartbeat did not discriminate clinical groups (Fig. 6B, E, C, and F).

3. Discussion

In a representative sample of patients using mental health services in the UK, we characterised interoception as the processing and representation of internal bodily physiology (Craig, 2002; Critchley and Harrison, 2013; Khalsa et al., 2018; Quadt et al., 2018; Tsakiris and Critchley, 2016). We predicted a transdiagnostic relationship between interoception and psychopathology (Ardizzi et al., 2016; Craig, 2002; Critchley and Harrison, 2013; Garfinkel et al., 2015a; Khalsa et al., 2018; Quadt et al., 2018; Schäfelein et al., 2018; Seth and Tsakiris, 2018;...
Fig. 4. Affective symptoms in patient and comparison participants. Distributions of subjective symptoms scores are shown for each group. (A) Depression scores in comparison and patient participants. (B) State anxiety scores in comparison and patient participants. (C) Trait anxiety scores in comparison and patient participants. (D) Depression scores in comparisons and patient diagnostic groups. (E) State anxiety scores in comparisons and patient diagnostic groups. (F) Trait anxiety scores in comparisons and patient diagnostic groups.
Tsakiris and Critchley, 2016; Tsakiris et al., 2011), especially anxiety symptoms, previously linked to differences in physiology (heart rate and heart rate variability (HRV)) (Chalmers et al., 2014; Kemp et al., 2017), heartbeat detection accuracy (Dunn et al., 2010b; Van der Does et al., 1997; Zoellner and Craske, 1999), self-reported bodily sensibility (Palser et al., 2018), and discrepancies between behavioural and self-report measures of interoception (Garfinkel et al., 2015b; Garfinkel et al., 2016).

We found that patients differed from comparison participants in cardiac physiology (HRV), interoceptive behavioural performance
accuracy and self-report trial-by-trial confidence, exhibiting reduced HRV, accuracy and confidence. However, after adjustment for age, gender and BMI, these statistically significant differences were only maintained for confidence and behavioural accuracy in the heartbeat discrimination task. Across patients, self-report interoception paralleled heart rate variability, heart rate; HRV = heartbeat tracking task; HBD = heartbeat discrimination task; acc = accuracy; conf = confidence; aware = awareness; BPQ = Porges Body Perception Questionnaire; ITPE = Interoceptive Trait Prediction Error. *Missing data.

Table 2
Differences between patient and comparison participants on cardiac physiological and interoceptive dimensions.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Before covariate adjustment</th>
<th>After covariate adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Comparisons</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>HR</td>
<td>73.08</td>
<td>11.6</td>
</tr>
<tr>
<td>HRV</td>
<td>51.60</td>
<td>24.6</td>
</tr>
<tr>
<td>HBT acc</td>
<td>0.48</td>
<td>0.4</td>
</tr>
<tr>
<td>HBT conf</td>
<td>4.20</td>
<td>2.5</td>
</tr>
<tr>
<td>HBT aware</td>
<td>0.21</td>
<td>0.5</td>
</tr>
<tr>
<td>HBD acc</td>
<td>0.52</td>
<td>0.1</td>
</tr>
<tr>
<td>HBD conf</td>
<td>4.97</td>
<td>2.4</td>
</tr>
<tr>
<td>HBD aware</td>
<td>0.52</td>
<td>0.1</td>
</tr>
<tr>
<td>BPQ aware</td>
<td>112.23</td>
<td>29.0</td>
</tr>
<tr>
<td>ITPE HBT</td>
<td>0.04</td>
<td>1.5</td>
</tr>
<tr>
<td>ITPE HBD</td>
<td>1.04</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Note: Results are from ANOVA and ANCOVA models. Notes: HR = heart rate; HRV = heart rate variability; HBT = heartbeat tracking task; HBD = heartbeat discrimination task; acc = accuracy; conf = confidence; aware = awareness; BPQ = Porges Body Perception Questionnaire; ITPE = Interoceptive Trait Prediction Error. *Correlation is significant at the 0.05 level.

This work suggests that specific symptoms in particular groups may be targetable through interoceptive training and even more heuristic tasks, leading to validated symptomatic improvement through interoceptive modification, even in comparison to active control conditions. Importantly, the BPQ-awareness questionnaire taps into different elements of interoception, namely, how aware one is of bodily signals, how often they are aware of bodily signals, and how accurately they perceive bodily signals (Gabriele et al., 2022). Thus, scores can differ depending on how participants interpret the questions. In the present study, patients and comparisons did not differ in terms of their BPQ-awareness scores and patient groups did not differ after consideration of covariates. The lack of difference could be due to a commonality of BPQ-awareness interpretation across groups revealing a lack of clinical difference, or it could result from differences in individual interpretation, potentially reflected in the spread of scores. Future studies should therefore provide clearer instructions and assess individual training to target anxiety in autistic adults (Quadt et al., 2021).
interpretations in order to improve the clarity of findings. In contrast, affective symptoms showed limited transdiagnostic association with cardiac physiology among patients, despite the established coupling between perseverative cognition (e.g., worry and rumination) and reduced HRV (Carnevali et al., 2018). Here, we observed no significant relationships between HRV and anxiety/depression symptom severity. Interestingly, we did observe HRV to be lower in diagnoses other than depression and/or anxiety disorder (see below) (Chalmers et al., 2014).

Our data also demonstrates differences in interoception between psychiatric diagnoses. First, our findings extend previous reports of markedly reduced HRV in patients with emotionally unstable/borderline personality disorder (Koenig et al., 2016), bipolar disorder (Hage et al., 2019) or schizophrenia/schizoaffective disorder (Roettger et al., 2006; Cacciotti-Saija et al., 2018). For schizophrenia/schizoaffective disorder, this effect has been seen in comparison to both healthy controls and controls with social anxiety (Cacciotti-Saija et al., 2018) or depression (Clamor et al., 2014), with psychosis being the primary diagnostic criterion. Given that psychosis is often present in both emotionally unstable and bipolar disorder, this could explain the reduced HRV observed in these groups. Lower HRV has been found to correspond to increased overall and negative symptom severity (e.g., reduced emotional expression) (Quintana et al., 2016). Because HRV indexes the modulation of perception of emotional and sensory cues, less heart rate responsivity may reflect vulnerability to dissociative states and depersonalisation. Trends toward faster mean heart rate and lower heartbeat tracking accuracy suggest more pervasive interoceptive differences in schizophrenia. They also hint at potentially elevated sympathetic activity in this group. Patients with schizophrenia and schizoaffective disorder were further differentiated by the schizoaffective patients significantly under-reporting sensitivity to bodily sensations (Garfinkel et al., 2015b). The clinical distinction between schizophrenia and schizoaffective disorder is rarely examined in research studies, favouring instead a broader diagnosis of psychosis. Although psychotic phenomena suggest disrupted self-representation (Ardizzi et al., 2016; Eccles et al., 2015; Insel et al., 2010; Schäfl et al., 2018; Seth and Tsakiris, 2018; Suzuki et al., 2013; Tsakiris et al., 2011), our study’s focus on transdiagnostic relationships between interoception and affective symptoms meant that we did not quantify psychotic and dissociative symptoms. However, antipsychotic medication and illness duration did not provide a compelling account for interoceptive differences in schizophrenia. Thus, our exploratory findings motivate further research to characterise symptoms of schizophrenia and schizoaffective disorder with attention to interoceptive profiles (Ardizzi et al., 2016).

Heartbeat detection tasks seek to quantify stable individual differences in sensitivity to cardiac sensations. Typically, the heartbeat counting task gives a spread of accuracy scores, while the more challenging heartbeat discrimination task produces a more binomial distribution (i.e., at chance, or above chance). Nevertheless, these tasks have recognised psychometric limitations (Brener and Ring, 2016; Desmedt et al., 2018). Actual heart rate, knowledge of one’s average heart rate, and the ability to estimate time, can influence performance accuracy, particularly on heartbeat tracking. The perceived signals themselves may be ‘quasi-interoceptive’, i.e., somatosensory correlates of the (visceral afferent) signalling of internal physiology (Desmedt et al., 2018). These factors can contaminate objective measurement of interoceptive sensitivity with beliefs and predictions about what ‘should be felt’ (Garfinkel et al., 2015b). Notwithstanding, heartbeat detection tasks remain relevant to inferences about how bodily sensations influence emotional states. For example, in non-clinical populations, heartbeat detection ability has been associated with increased anxiety symptoms, yet attenuated depressive symptoms (Dunn et al., 2010a; Dunn et al., 2010b), although further investigation of these relationships is required (Adams et al., 2022). Moreover, the relevance of heartbeat detection task performance accuracy to measures of psychiatric symptoms has been called into question by a recent meta-analysis of studies, many involving clinical patients with affective disorders (Desmedt et al., 2022). While reduced interoceptive accuracy is reported in patients with schizophrenia, and replicated in our present study, previous work demonstrates that the presence of positive symptoms correlates with better heartbeat detection accuracy (Ardizzi et al., 2016). Within our

### Table 3

Selected correlations between affective symptoms and interoceptive measures in patient and comparison participants.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Before covariate adjustment</th>
<th>After covariate adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BDI</td>
<td>STAI-Y1</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAI-Y1</td>
<td>0.519***</td>
<td>0.640***</td>
</tr>
<tr>
<td>n</td>
<td>306</td>
<td>306</td>
</tr>
<tr>
<td>STAI-Y2</td>
<td>0.752***</td>
<td>0.640***</td>
</tr>
<tr>
<td>n</td>
<td>306</td>
<td>306</td>
</tr>
<tr>
<td>HBD aware</td>
<td>0.104</td>
<td>0.188**</td>
</tr>
<tr>
<td>n</td>
<td>285</td>
<td>284</td>
</tr>
<tr>
<td>BPQ aware</td>
<td>0.353***</td>
<td>0.393***</td>
</tr>
<tr>
<td>n</td>
<td>282</td>
<td>282</td>
</tr>
<tr>
<td>ITPE HBT</td>
<td>0.236***</td>
<td>0.204***</td>
</tr>
<tr>
<td>n</td>
<td>270</td>
<td>270</td>
</tr>
<tr>
<td>ITPE HBD</td>
<td>0.162**</td>
<td>0.247***</td>
</tr>
<tr>
<td>n</td>
<td>270</td>
<td>270</td>
</tr>
</tbody>
</table>

Comparisons

| STAI-Y1 | 0.279 | 0.424** | 0.640*** |
| n | 43 | 41 | 41 |
| STAI-Y2 | 0.535*** | 0.579*** | 0.545*** |
| n | 43 | 65 | 41 |
| HR | –0.013 | 0.302* | 0.107 |
| n | 43 | 43 | 41 |
| HBD conf | –0.166 | –0.324* | –0.262 |
| n | 43 | 43 | 41 |

Note: Data are Spearman’s rho values with n = sample size. Key: *Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed); ***Correlation is significant at the 0.001 level (2-tailed); BDI = Beck Depression Inventory; STAI = Spielberger State and Trait Anxiety Inventory, Y1 = state, Y2 = trait. HR = heart rate; HRV = heart rate variability; HBT = heartbeat tracking task; HBD = heartbeat discrimination task; acc = accuracy; conf = confidence; aware = awareness; BPQ = Porges Body Perception Questionnaire; ITPE = Interoceptive Trait Prediction Error. Correlations not shown were not significant.
study, patient participants performed worse than comparison participants on the heartbeat discrimination task, and though among patient groups performance accuracy was broadly equivalent, schizophrenia patients tended to perform worse. While interoceptive methods can be further optimised for patient stratification, we demonstrate reliable implementation of heartbeat detection tasks within clinical settings.

In psychiatry, interoception is often an indirect target of treatment. Medications influence interoceptive processes; e.g., peripheral cardiovascular arousal is suppressed by beta-blockers, while monoaminergic drugs (from stimulants in ADHD, to antidepressant/anxiolytic SNRIs) target central neuromodulatory pathways governing central arousal and descending autonomic control. Trials repurposing antihypertensive
drugs, e.g., Losartan (Zhou et al., 2019), and research on interoceptive immune-brain and gut-brain signalling (Bell et al., 2017; Critchley and Harrison, 2013; Cryan et al., 2019; Krishnas and Harrison, 2016) promise alternative treatment approaches. Non-pharmacological therapies also exploit interoceptive mechanisms. These include physical interventions, notably vagus nerve stimulation (Conway and Xiong, 2018) and flotation therapy (Feinstein et al., 2018), bio-behavioural therapies (e.g., autonomic biofeedback training) (Nagai, 2015), and integrative interventions (e.g., mindfulness and yoga) (Bornemann et al., 2015; Mehling et al., 2018). Many treatments, including beta-blockers, bio-behavioural therapies and exercise training work to increase heart rate variability (Nolan et al., 2008). The therapeutic utility of each of these approaches can be optimised through better mechanistic understanding of interoceptive processing on the individual level. Arguably, the efficacy of these treatments rests in their indirect targeting of interoceptive processes through (neuro)physiological and/or interoceptive pathways (Nord and Garfinkel, 2022). These pathways effect changes in the body, including neural modulation and autonomic processing, often upregulating or downregulating the sensation and perception of bodily signals. For mental health conditions, this can lead to attenuation of symptoms. In the long term, effective recalibration of internal signalling can lead to recovery.

Moving forward, there is great need for new methods which patients can perform without undue burden (e.g., consisting of manageable numbers of trials in engaging tasks designed to limit fatigue) and tapping into specific aspects relevant to each individual patient’s condition. Examples of such approaches include implicit measures such as heartbeat evoked potentials (Petschner et al., 2019; Pollatos and Schandry, 2004; Yuan et al., 2007) and cardiac timing effects (Garfinkel et al., 2020), as well as more explicit heartbeat detection tasks and questionnaires (Gabriele et al., 2022; Murphy et al., 2020). The explicit techniques presented here have the added advantage of being adaptable to remote settings, allowing patients to participate in therapy from a location of their choice. These approaches are especially important considering the growing need for practical, flexible, and effective mental health treatments.

Outside of cardiac interoception, there is a growing understanding of the influence of additional interoceptive signals including respiration, gastric activity, and immune system activation on mental health. For example, respiratory studies have shown that slow, nasal breathing increases gastric activity, and immune system activation on mental health. For conditions showing sensitivity to the effects of different interoceptive signals (Sterling, 2014). As interoception serves not only to inform the brain of the body-state, but to also enhance allostatic and homeostatic regulation, there is a need for more studies which explicitly perturb both allostatic and homeostasis, assessing interoceptive dysfunction across a fuller range of functionality (Khalsa et al., 2018). Several perturbative interventions suggest potential for these methods to improve aspects of interoception and autonomic functioning (De Couck et al., 2017; Janssen et al., 2016; Kox et al., 2014; Quadt et al., 2021; Van Diest et al., 2005). However, comparison of these methods to more commonly used resting-state methods would be useful, as well as consideration of these and future methods for particular psychiatric conditions.

This study follows a rising call for interoceptive processes to be considered foundational to psychiatric conditions (Khalsa et al., 2018; Smith et al., 2021). We show the feasibility of a multilevel characterisation of interoception in patients spanning diagnostic categories. Our findings reveal transdiagnostic interoceptive profiles linked to affective symptoms and suggest interoceptive measures may differentiate certain patients by diagnosis. Notably, there are potentially selective differences in patients with schizophrenia that merit further investigation. Interoception thereby offers emerging targets for therapeutic intervention in psychiatric conditions.

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CRediT authorship contribution statement

All authors except AMJ, SPS and LQ contributed to the design of the study. FM, DLE, CGvdP, HHB carried out data collection and management with trained clinical research coordinators employed by Sussex Partnership NHS Foundation Trust. SNG and HDC wrote the first manuscript draft. SPS analysed data and produced figs. HDC, SPS, SNG, JAE, LQ and AMJ contributed to the final manuscript. All authors read and approved the final manuscript.

Data availability

Data are shared as supplementary material.

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Appendix A. Supplementary data

Fully anonymised data are available as supplementary information. Supplementary data to this article can be found online at https://doi.org/10.1016/j.autneu.2023.103072.

References


